How to Diagnose The Red Eye

You know us for tonometry.

Get to know iCare for imaging and perimetry.

Discover the next level of eye care with our full line of devices.

Scan or visit www.icare-world.com/USA
iCare COMPASS

More than a standard perimeter

Unique technology combining a visual field test with fundus imaging

Active retinal tracking compensates for eye movements creating reliable, repeatable results

Auto-focus capability omits the need for trial lenses eliminating ring artifacts

Discover the next level of eye care with our full line of devices.
Scan or visit www.icare-world.com/USA
How to Diagnose The Red Eye

With careful examination and history-taking, most unusual causes of red eye can be uncovered. P. 40

Also inside
• Dry-eye Treatment Continues to Evolve P. 24
• How Experts Evaluate the Dry-eye Patient P. 34
• IOL Fixation: Tried-and-True Techniques P. 48
Start with EYSUVIS® – the first and only FDA-approved corticosteroid for the short-term treatment of dry eye (up to 2 weeks). EYSUVIS®, with proprietary AMPPLIFY Drug Delivery Technology, is designed to deliver loteprednol nanoparticles to the sites of ocular surface inflammation, where dry eye flares start.

EYSUVIS® goes to work fast and provides rapid improvement of ocular discomfort, with results as early as Day 4 after starting treatment.

Go deep to treat dry eye with EYSUVIS®

The safety and efficacy of EYSUVIS® was assessed in 4 multicentered, randomized, double masked, placebo-controlled trials in 2,871 patients with documented Dry Eye Disease. Patients received either EYSUVIS® or vehicle 4 times a day for at least 2 weeks. In one Phase 3 study, patients using EYSUVIS® showed significant reduction in the symptoms of dry eye (ocular discomfort) as early as Day 4 after starting treatment (vs. vehicle). Symptom improvement continued up to the end of the treatment period (Day 15, primary endpoint). Patients using EYSUVIS® also showed significant reduction in signs of dry eye (conjunctival hyperemia) at Day 15 vs. vehicle.

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

INDICATION
EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

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

Warnings and Precautions:
Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

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

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.

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

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

Adverse Reactions:
The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

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


© 2023 Alcon Inc. 07/23 US-EYS-2300027
Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominata artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A perinatal/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg. Lactation—There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for EYSUVIS and any potential adverse effects on the breastfed infant from EYSUVIS. Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Geriatric Use—No overall differences in safety and effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (TK) assay, and in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.eysuvis-ecp.com/

Manufactured for:
Kala Pharmaceuticals, Inc.
Watertown, MA 02472

Marks designated by ™ or © are owned by Kala Pharmaceuticals, Inc. Patented. WWW.KALARX.COM/PATENTS

© 2020 Kala Pharmaceuticals, Inc. All rights reserved. US-EYS-2300027

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

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

WARNINGS AND PRECAUTIONS
Delayed Healing and Corneal Perforation—Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin cornea or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP. Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation. Bacterial Infections—Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection. Viral Infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ophthalmic corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal Infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate. Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension. Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic corticosteroids include elevated intraocular pressure, which may be associated with intregun optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Clinical Trials Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS
Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20% of clinically recognized pregnancies. Data: Animal Data. Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis.
The suggested workforce-to-population ratio required for adequate delivery of neuro-ophthalmology services has been estimated to be one specialist per 1.2 million people. However, in 2022 only eight U.S. states met this threshold; in the worst-served areas, six had no neuro-ophthalmologists in the entire state. With increasing outpatient demand, and the subspecialty’s scarcity, one new study wanted to determine what the typical presentations to the emergency department for related issues look like. The prospective study published in *Ophthalmology* included one academic care institution’s ED and inpatient neuro-ophthalmology consultation patterns and patient outcomes over one year. Of the 494 consecutive adult consultations, 49 percent took place at night or on weekends. Of the emergency consults (65 percent), 39 percent of these occurred during weekdays, 39 percent on weekends and 22 percent on weekends/holidays. Of 322 ED consultations, 70 percent presented with a chief neuro-ophthalmic complaint. Referrals to the ED by health-care professionals were primarily made by eye-care specialists (76 percent, 196 patients). Most commonly encountered questions for emergency referral were due to papilledema at 23 percent and vision loss at 22 percent. A sizable 68 percent had a final active neuro-ophthalmic diagnosis, 69 percent had high or very high complexity and 44 percent needed admission. Of the remaining 172 inpatient consultations, most were requested by hospitalists, including neurologists (41 percent) and oncologists (12 percent) for vision loss (25 percent) and eye movement disorders (20 percent), as well as neurosurgery (33 percent) to examine for mass or preoperative evaluation (11 percent). Active neuro-ophthalmic diagnosis was confirmed in 67 percent of patients, and a striking 90 percent of cases found neuro-ophthalmic assessment appropriate to make a diagnosis or evaluate for ophthalmic manifestations of disease. Follow-up with outpatient neuro-ophthalmology was required in 59 percent of patients. The study authors note that overall, 61 percent of patients were diagnosed with a life- or vision-threatening pathology. Of the 49 percent of consultations occurring during off-hours, only 25 percent of these were urgent—highlighting the paradoxical relationship between the additional burden generated by these unscheduled urgent neuro-ophthalmology consultations and the genuine need for these patients to be examined by a neuro-ophthalmologist, to whom limited access generates more such consultations.”

Driving the spikes in neuro-ophthalmology referrals or consultations are factors of delayed consultations resulting in diagnostic errors, increased cost and worse outcomes, made worse by associated risk for litigation for the provider if not done promptly. Further motivation for patient referral to hospitals than outpatient clinics is that ED or hospital evaluation is time efficient, which allows for immediate multidisciplinary care and testing which may be delayed otherwise with outpatient settings.

To deal with the rising rates, the authors propose that increasing the number of available outpatient neuro-ophthalmologists may be one solution. They also propose that “there is a need for expanded development and utilization of technological and diagnostic aids such as nonmydriatic fundus cameras in EDs as well as telehealth...
Your Complete Resource.

ARCHITECTURE · SPACE PLANNING · FRAME DISPLAYS · DISPENSING FURNITURE

YOUR FOCUS IS ON THE BUSINESS OF OPTICAL

A New VISION in Optical Management.

VENTURE OPTICAL MANAGEMENT

800-346-8890 · www.eyedesigns.com

VENTURE OPTICAL MANAGEMENT

delivery processes for integration into health-care settings. Finally, creating and implementing standardized neuro-ophthalmology ED and hospital protocols for commonly encountered presentations and diseases should facilitate rapid diagnosis and treatment of common neuro-ophthalmologic disorders."


Apellis Gives Update on Syfovre Safety Issues

On the heels of several class action lawsuits filed against it as a result of reported safety events involving Syfovre (pegcetacoplan injection), Apellis Pharmaceuticals provided an update on company-supplied injection kits and an update on events of retinal vasculitis reported in real-world treatment with Syfovre for geographic atrophy secondary to age-related macular degeneration.

According to Apellis, eight events of retinal vasculitis (five occlusive, three non-occlusive) have been confirmed. The last confirmed event of retinal vasculitis occurred on June 20. There are also two other cases of unconfirmed retinal vasculitis from May and August.

Here is an update on the injection kits from the company:

As part of the company’s investigation into real-world safety events, internal structural variations were identified in the specific 19-ga x 1.5-inch filter needle included in certain injection kits. Filter needles are used to withdraw treatment from the vial when preparing for an injection procedure. A causal relationship has not been established between the structural variations in this 19-ga filter needle and the rare events of retinal vasculitis in the real world. The company recommends that practitioners immediately discontinue use of any injection kits that contain the 19-ga filter needle and use injection kits with the 18-ga filter needle, which are already in distribution. While injection kits previously contained one of two types of filter needles (either 18- or 19-ga), Apellis is now exclusively distributing injection kits with the 18-ga filter needle.

Durango, Colorado, retina specialist Sara Haug says she’s following the company’s guidance, but that others might seek other options. “I can’t imagine the filter needles were the culprit but I have switched to using the 18-ga filter needle they suggest,” she opines. “I have also not stopped using Syfovre due to the cases of vasculitis, since the number of patients having this complication has been so low. Compared to brolucizumab which had a 1 to 2 percent complication rate, the complication rate so far with Syfovre is around 0.01 percent, I believe. I have colleagues who have stopped using Syfovre, however, due to the complications, and haven’t restarted even with the information about the filter needle. Honestly, it’s a bit hard to know what to make of it all, and I’m guessing a lot of us will switch to Izervay, as that is now approved.”

Weak Relationship Between Dry Eye Signs and Symptoms

The list of potential ocular manifestations associated with dry eye disease (DED) are non-specific, comprising redness, burning, stinging, foreign body sensation, photophobia and pruritis. While DED diagnosis is dependent upon reports of ocular symptoms and measurements of signs, literature has not clearly demonstrated a link between signs and symptoms. One new study assessed this need by determining correlations among symptoms and signs of dry eye in the Dry Eye Assessment and Management (DREAM) study.1

Moderate to severe dry eye was assessed in a total of 535 patients, using the Ocular Surface Disease Index (OSDI) for symptoms. Four DED signs were tested in both eyes, including conjunctival lissamine green staining, corneal fluorescein staining, Schirmer’s testing and tear breakup time following standard protocol at baseline and follow-up visits at three, six and 12 months.

The researchers found OSDI scores at baseline didn’t correlate with signs, but OSDI subscale score of ocular symptoms was weakly associated with corneal staining score and Schirmer test score. There were correlations among the four signs. Correlations among changes in signs and symptoms were weaker, with the highest correlation being between change in conjunctival staining and corneal staining. Overall, the results yielded low correlation of DED symptoms with signs, even weaker correlation among changes in symptoms and signs, but low to moderate correlation among the four signs.

The study researchers, as part of their discussion, relay that the weak associations observed may be due to comorbidities that could increase the percep-
tion of ocular symptoms in dry-eye patients, such as with neuropathic pain or other chronic pain conditions. They also mention that although the OSDI subscale and ocular symptoms displayed weak association with corneal staining and Schirmer’s test scores, these correlations didn’t differ with sex or depression status, although were stronger in patients with Sjögren’s syndrome. Similarly, despite low correlations among the four signs of dry eye, the highest correlation was seen with corneal and conjunctival staining and was higher in the population of patients with Sjögren’s.

The authors discuss how mental health disorders can also contribute to the symptom level experienced with DED, which aren’t consistent with the severity of DED signs. One previous study outlined that DREAM participants with depression experienced more severe dry-eye symptoms than those without. Another observed depression to be more prevalent in DED patients and was associated with symptoms of dry eye but not signs. The current study found that the correlation was weaker between dry-eye signs and symptoms for those with depression than those without. As such, this may play a part in some of the discordance seen between signs and symptoms, but offers no complete explanation, and is likely not the majority of causation of these findings. These observations prompt the authors to convey that “better objective minimally invasive metrics that capture biologic changes in the eye might lead to a better assessment of the severity of ocular surface changes in DED and perhaps a better correlation with symptoms.”


**Cataract Surgery a Boon in Acute Angle Closure Glaucoma**

Sudden pressure increases that accompany acute angle closure can have devastating visual consequences. Prompt treatment is required to re-open the angle, often consisting of laser peripheral iridotomy to improve pupillary block. This approach doesn’t always open up narrow angles, however. Removing the lens via phacoemulsification is an alternative approach for deepening the anterior chamber, and in fact, a recent article published in the *Journal of Cataract and Refractive Surgery* reported that phaco was both safe and effective for this purpose. The study included 50 eyes of patients who underwent phaco within a week of presenting with acute angle-closure glaucoma and receiving IOP lowering treatment. All eyes were imaged and measured using anterior segment OCT and Pentacam. The mean preoperative IOP was 40.3 mm Hg, which decreased to 14.9 mm Hg within one week of operation. Further pressure lowering was observed at postop weeks four and 12, to 12.4 and 11.44 mmHg, respectively. The mean preoperative temporal angle width was 18.13˚, which widened respectively to 32.6˚, 34.6˚ and 36.2˚ at one, four and 12 weeks postop. The mean preoperative nasal angle width also increased from 17.8˚ to 32.7˚, 34.5˚ and 36.2˚ at postop weeks one, four and 12, respectively.

The researchers conclude in their paper that “early phacoemulsification is very effective in treating acute angle-closure glaucoma cases immediately after medical control of high intraocular pressure and resolution of corneal edema.”


**INDUSTRY NEWS**

**FDA Approves Eylea HD Injection 8 Mg for Treatment of Wet AMD, DME & DR**

Regeneron Pharmaceuticals announced the FDA approved Eylea HD (afibercept) Injection 8 mg for the treatment of patients with age-related macular degeneration, diabetic macular edema and diabetic retinopathy. The recommended dose for Eylea HD is 8 mg (0.07 mL of 114.3 mg/mL solution) every four weeks (monthly) for the first three months across all indications, followed by 8 mg every eight to 16 weeks in wAMD and DME, and every eight to 12 weeks for DR.

**Iveric Bio/Astellas Receives FDA Nod for Izervay Treatment for GA**

Last month, Astellas Pharma announced that the FDA approved Izervay (avacincaptad pegol) for the treatment of geographic atrophy secondary to AMD. The company says Izervay, a new complement C5 inhibitor, is the only approved GA treatment with a statistically significant reduction (p<0.01) in the rate of geographic atrophy progression at the 12-month primary endpoint across two Phase III trials.

**Oculis Announces Findings for OCS-01 in Phase III OPTIMIZE**

Oculis announced topline results from its Phase III OPTIMIZE clinical trial with OCS-01 eye drops, which the company describes as a novel, once-daily, high-concentration, preservative-free, topical Optireach formulation of dexamethasone for the treatment of inflammation and pain following ocular surgery.

**Harrow To Sell Vigamox in the United States**

Harrow received the rights to the New Drug Application for the antibiotic Vigamox (first approved in 2003). Harrow purchased the U.S. commercial rights to Vigamox in January 2023.
Keeler

Take a second look at Keeler

In collaboration with clinicians, and using our expertise, Keeler are delivering new enhancements to improve yours and your patient's experience.

The next evolution in slit lamps

• Keeler Konnect digital imaging software now comes with DICOM capabilities, so you can integrate your slit lamp into your patient management system.
• 14mm slit aperture allows you to see a larger area of the retina.
• Finer slit width diaphragm scale enabling you to precisely measure pathologies, within even smaller increments.
24
Dry-eye Treatments Continue to Evolve
Every year, clinicians’ understanding of dry-eye disease changes as more findings and treatments surface in eye care.
Andrew Beers
Associate Editor

34
How the Experts Diagnose Dry Eye
Grading the severity of dry eye by assessing signs and symptoms helps ophthalmologists treat and follow dry-eye patients.
Michelle Stephenson
Contributing Editor

48
IOL Fixation: Tried-and-true Techniques
When faced with lack of capsular support, cataract surgeons have a variety of options to secure an IOL, each with its own strengths and flaws, say experts.
Liz Hunter
Senior Editor
DEPARTMENTS

September 2023

4
News

12
EDITOR'S PAGE
Summer Blockbusters
Walter Bethke
Editor in Chief

16
REFRACTIVE/CATARACT RUNDOWN
LASIK Enhancements: Handle with Care
Refractive surgeons say the keys to managing these cases are patience and precision.
Liz Hunter, Senior Editor

23
THE FORUM
The March of Time
Mark H. Blecher, MD
Chief Medical Editor

57
GLAUCOMA MANAGEMENT
Managing Steroid-Induced Glaucoma
This secondary glaucoma has a unique pathophysiology that may inform treatment approaches.
Douglas J. Rhee, MD

61
RETINAL INSIDER
An Update on Fundus Autofluorescence
This imaging method can help elucidate retinal disease, monitor progression and help advance therapy.
Yse Borella, MD, Harshit Vaidya, MD and Jay Chhablani, MD

69
TECHNOLOGY UPDATE
Help for Intravitreal Injections
Traditional intravitreal injection techniques are tried-and-true, but there are devices that can help guide the procedure.
Andrew Beers
Associate Editor

71
AD INDEX

72
WILLS EYE RESIDENT CASE SERIES
A young woman presents with sudden-onset blurred vision and metamorphopsia in one eye.
Mara E. Penne, MD, and Carol L. Shields, MD

VISIT US ON SOCIAL MEDIA
Facebook www.facebook.com/RevOphth
Twitter/X twitter.com/RevOphth
Instagram @revophth
NOW AVAILABLE TO PRESCRIBE

Tarsus, XDEMVy, and the associated logos are trademarks of Tarsus Pharmaceuticals, Inc. © 2023 Tarsus Pharmaceuticals, Inc. US--2300350 9/23
When you hear the term "summer blockbuster," you think of a movie like the box-office juggernaut "Barbie." However, there are other kinds of blockbusters, too—the kind that, in addition to raking in $16 billion in one year, can transform our behavior and our waistlines. I'm talking about the weight-loss drugs Ozempic and Wegovy (both semaglutide) from Novo Nordisk. The buzz around these two meds really kicked into overdrive this summer with the revelation of positive study findings such as semaglutide's ability to cut cardiovascular events by 20 percent1 and give renewed vigor to heart-failure patients.2

The drugs' success is affecting the business world, too, sending companies associated with diabetes therapy and obesity scrambling. For instance, the value of Medifast, a company that provides weight-loss programs, dropped 26 percent. Insulin-pump makers are also hurting, and the maker of the DaVinci robotic surgery system, which is used in bariatric procedures, says the drugs are cutting into patient demand—some patients just don't need the surgery now.3

However, there are potential negatives with these wonder drugs. First, as pointed out in a recent JAMA commentary, the drugs' success is hamstringing our desire to study the actual roots of obesity. Why do the hard work on the topic when patients can just get an injection?4

"Big pharma can come up with a billion dollars to take a promising drug through Phase III clinical trials without difficulty because the profits can be enormous," wrote David S. Ludwig, MD, PhD, an endocrinologist and researcher at Boston Children's Hospital, "whereas researchers trying to understand the environmental and dietary drivers of obesity must manage with a shoestring budget."4

In ophthalmology, paradoxically, the increased use of semaglutide may result in increased complications related to diabetic retinopathy, according to the results of the SUSTAIN 6 trial, though increases in DR appear to be transient. Probably the most pressing issue—as it almost always is—is cost. These drugs cost $10,000 to $15,000 per year, which has the potential to increase U.S. healthcare spending by 50 percent. However, now there are rumblings that Medicare may start paying for the drugs for some patients—but analysts say that could be disastrous; at the drugs' current cost, paying for 100 million obese patients could potentially bankrupt Medicare.3 Where will the money come from? Hopefully, if Medicare gets involved, CMS won't start eyeing cataract surgery or other ophthalmic procedures, because everything in those arenas has been cut to the bone.

The situation probably calls for proactive interactions with lawmakers to reinforce the idea that cataract surgery is a service that's of tremendous value to patients. Maybe an ophthalmology blockbuster is in order?

I can see it now: "Cataract Surgery 2: This Time, It's Personal."

— Walter Bethke
Editor in Chief

3. Wainer D. The Ozempic craze could put these companies on a crash diet. WSJ. August 18, 2023.
Complete and long-lasting resolution of NK for most patients*1-4

- **Up to 72% of patients** achieved complete corneal healing in clinical trials*1-3
- **80% of these patients** remained healed at 1 year (REPARO trial)†4

* Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.1-3
† Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 European patients with neurotrophic keratitis (NK) in 1 eye per group; 72% of patients completely healed; vehicle response rate 33.3%. Study NGF0214: 24 US patients with NK in 1 or both eyes per group; 65.2% completely healed; vehicle response rate 16.7.*2,3

**Important Safety Information**

**WARNINGS AND PRECAUTIONS**

**Use with Contact Lens**
Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

**Eye Discomfort**
OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

**ADVERSE REACTIONS**
In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1% to 10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**
There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

**Lactation**
The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

**Pediatric Use**
The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

**INDICATION**
OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

**DOSAGE AND ADMINISTRATION**
Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

**References:**

See more clinical data OXERVATE.com/hcp
Brief Summary of full Prescribing Information
Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE
OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION
General Dosing Information
Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.
If a dose is missed, treatment should be continued as normal, at the next scheduled administration.
If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.
Recommended Dosage and Dose Administration
Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

WARNINGS AND PRECAUTIONS
Use with Contact Lens
Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort
OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.
In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.
Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Lactation
Risk Summary
There are no data on the presence of OXERVATE in human milk, the effects on breastfeeding, infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use
The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use
Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis and Mutagenesis
Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility
Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).
In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

Risk Summary

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfeeding, infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).
In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

Risk Summary

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfeeding, infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).
In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

Risk Summary

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfeeding, infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).
In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).
Despite LASIK’s accuracy, enhancements simply come with the territory. Every once in a while a target is missed or a patient from years ago will show up with visual complaints and refractive surgeons must consider time, technique and potential risks of retreatment. We asked some veteran refractive surgeons for their insight and pearls for these rare but unavoidable situations.

Reasons for Enhancements
Enhancements typically fall into two categories: early and late. Early enhancements take place within the first few months of the initial LASIK procedure, usually due to a refractive miss that was noticed quickly following surgery. Late enhancements happen years down the line as a result of changes in the patient’s natural lens.

Regarding early enhancements, “If the patient’s unhappy with their vision in the early postop period, and you missed the target by 0.75 to 1 D, our objective at that point is to get them through that two to three month period,” says Scott MacRae, MD, the director of refractive services in the department of ophthalmology at the University of Rochester. “Many times we’ll fit them with a soft contact lens so they can see better, particularly for patients who are overcorrected and hyperopic in the presbyopic age group. Those patients can really struggle, but fitting them with a hyperopic soft contact lens in that early postop period can help them get back to a much more functional state for going back to the office/daily activities. We try to nurse them through that two to three month period.”

Reliable measurements are critical in this early enhancement phase, continues Dr. MacRae. “If somebody’s really having a hard time, you could consider retreatring at two months postop but you probably want two or three measurements before you actually go ahead and do your retreatment, particularly in patients who don’t have a real clear endpoint. Sometimes they’re still changing. That’s more true for dry eyes and hyperopic correction than with myopic correction. Usually myopic correction is relatively stable after the first week or two after the dryness issues clear up,” he says. “If the patients are still dry at two or three months postop and you’re not getting reliable refractions, make sure that you aggressively treat the dryness before you get your final numbers and proceed with retreatment.”

Sometimes, the neuroadaptation of the patient needs to be considered and explained. “My tendency is that if the patient is 20/happy and I’m really close to the target, then I don’t encourage the patient to have retreatment
No two patients’ eyes are the same. That’s why REFRESH® provides a portfolio of products expertly formulated around your patients’ specific needs.

RECOMMEND THE LEADER IN PRESERVATIVE-FREE*

orefreshbrand.com/doc

*REFRESH® Family of Products. Ipsos Healthcare, 2021 REFRESH® ECP Recommendation Survey © 2023 AbbVie. All rights reserved. All trademarks are the property of their respective owners.
REFRACTIVE/CATARACT RUNDOWN

Figure 2. Scott MacRae, MD, developed an instrument called the MacRae Flap Flipper that allows him to gently lift and separate the LASIK flap, which he says has made epithelial ingrowth a rare occurrence.

unless they’re really insistent,” says Dr. MacRae. “If they’re insistent, then there are some tricks to that. Typically I’ll go ahead and refract them myself, or have my trusted staff refract the patient. Then we put that prescription into a spectacle trial frame and actually have the patient look at the difference compared to their uncorrected vision in each eye. If they notice a pretty significant visual improvement subjectively then I’ll go ahead and retreat, even if it’s relatively minor.

“The optics are more complicated than just simple numbers—there’s image quality, which can be affected by higher order aberrations or other subtleties that the patient is perceiving,” he continues. “Certain patients are much more neuroadaptive to their vision than others, so some patients can tolerate a small amount of refractive error, while other patients are really insistent that their image quality isn’t good enough and they want an improvement.”

Setting them up in a spectacle trial can be helpful in comparing each uncorrected eye to the best corrected vision with the trial lens. “If they don’t notice a difference, then I say, ‘If we try to go back and retreat, I don’t think it’s going to make any improvement,’” says Dr. MacRae. “Sometimes that’s enough for the patient to say, ‘My vision is pretty good. I’m happy.’ The doctor tried to do everything they can to get me the best vision I can get and I can settle for this.”

Doing the trial lens is actually really helpful because it avoids that situation where you go ahead and retreat, but then the patient doesn’t notice any difference and you’ve gone through this whole process. It really saves everybody time.

In cases of late enhancements, Louisville, Kentucky’s Asim Piracha, MD, says, “You have to consider why they need an enhancement two, three or five years later. It’s not that the LASIK ‘wore off’ or that the initial treatment didn’t work—it’s that something has changed to make them either myopic or hyperopic. For myopes, it’s even still more uncommon because their vision is pretty stable long term, and for hyperopes, they tend to get a bit more hyperopic over time. So, if you have a hyperope, usually they have a lot of accommodation and, as they get older, they lose accommodation which makes them more hyperopic. This may be the reason for the enhancement.”

Topography will reveal a wealth of information. “If they’re beyond a couple years out and they have a myopic astigmatic change, my first thought is to see if there is any ectasia,” Dr. Piracha says. “Before any enhancement you must be really careful to make sure their topography is normal and there’s no sign of even subtle ectasia. We like to look at the preop topography and postop topography to see what’s changed. If there’s any progressive myopia, astigmatism or steepening of the inferior cornea, bullous keratopathy on the surface or posterior surface, then we’re concerned about ectasia.

“For those patients you have to be cautious and have them come back in six months and make sure there are no progressive changes,” he continues. “If it’s completely stable and there’s any concern at all about ectasia, then I would only enhance with surface ablation, I wouldn’t lift the flap. If there are signs of ectasia progression I wouldn’t enhance them at all and I would do a cross-linking treatment to stabilize the cornea and then consider going back and doing a surface treatment to enhance them (ASA or PRK) once they’re stable, which I’m pretty cautious in waiting at least a year but ideally 18 months after cross-linking before doing any enhancement.”

Dr. Piracha takes a different approach if the patient is hyperopic. “Usually it’s not a sign of ectasia,” he says. “Typically it’s a loss of accommodation as they get older or their near vision is an issue. If they’re over 40 and hyperopic I’d possibly offer an enhancement, monovision or even a refractive lens exchange to enhance them vs. laser vision correction. In all patients after 40 and definitely after 45, I do wavefront measurements on the iTrace of their eyes and look for any dysfunctional lens syndrome—aberrations in the cornea vs. aberrations from their natural lens. That influences whether we pursue a lens exchange or not.”

Cataract development could also be contributing to their vision changes, notes Dr. MacRae. “If it’s an early cataract and we think that it’s progressing, we’ll recommend waiting for six to 12 months and seeing whether their refraction changes,” he says. “If the refraction is changing then it’s not a good time to go ahead and treat—you want to make sure that the refraction is stabilized. If they continue to prog-
ress and their refraction continues to change then we recommend cataract surgery or refractive lens exchange.”

**Treatments and Techniques**

Surgeons traditionally treat LASIK enhancements with PRK or by re-lifting the flap and ablating the bed. Whether the patient falls under the early or late enhancement category plays a major role in the decision.

“If they’re less than two years out, I typically lift the flap and enhance them,” says Dr. Piracha. “If the patient’s beyond two years there are definitely several studies and reports to show a higher rate for epithelial ingrowth.”

Dr. MacRae concurs. “I’ll go back and retreat with a flap lift up to about two years postop but avoid it after that since epithelial ingrowth is more common with flap lifting after the first few years postop,” he says. “After two years post LASIK, typically I’ll go and do PRK on a retreat. Sometimes, we’ll see patients that are 10 or 15 years postop and they still have a little residual refractive error and they come back for just a small tune up, in which case I’ll do PRK on those eyes as well.”

**PRK**

For his PRK retreats, Dr. MacRae has a process, beginning with an 8.5-mm corneal trephine to demarcate the epithelium he wants to remove centrally vs. what he wants to preserve peripherally. “It very accurately demarcates the edge of the epithelium that you’re taking off so you don’t have scrolls and other irregularities,” he says. He uses an 8.5-mm well filled with 20% alcohol over the area and lets it sit on the cornea for 40 seconds. “Before removing the well, I use a Weck-Cel and allow it to swell. Then I gently twirl the Weck-Cel,” he continues. “The twirling motion causes those lateral adhesions of the epithelium to continue to adhere but the vertical epithelium anchor actually breaks or dehisces, in which case you’ll have a swirl of epithelium that comes off very easily. Then, I just take a Maloney spatula and gently remove the epithelium until I get to the edge of the area.”

One of the problems with treating or retreating with PRK is that patients can get recurrent erosions from loose epithelium, says Dr. MacRae. “PRK (or LASIK) can create mild erosion symptoms from the epithelium not vertically anchoring well. On all PRK and PTK retreats that I do, I use mitomycin-C prior to inserting the TSCL. Even if there’s a 1 percent haze rate we’d rather have to have to deal with that at all.”

If you do notice scrolling of the epithelium, or it’s breaking down and not doing well, Dr. MacRae uses a Johnston applanator to smooth and stretch the flap. “If you notice the epithelium starting to loosen, use the Johnston applanator to appenate and stretch the flap, rather than trying to stretch the flap with Weck-Cels,” he says. “This instrument is a great option with friable epithelium and eyes with unrecognized anterior basement membrane disease to avoid damaging the epithelium further.

“Following treatment or retreatment with the excimer laser, I insert a bandage soft contact lens for seven to 10 days—sometimes, we might even leave it on longer,” he continues. “We used to worry about infection with a therapeutic soft contact lens but that’s an extremely rare event, as long as the patients are treated with antibiotics and they’re well instructed in terms of good hand-washing, rinsing the eye out in the morning with artificial tears and avoiding dust and dirt for that first week. After the bandage lens is removed, we put them on Muro 128 or a generic equivalent hypertonic ointment at bedtime for two months. This prevents recurrent erosion.”

**Re-lifting the Flap**

However, PRK doesn’t always make sense, even for late enhancements, notes Richard J. Mackool, MD, the founder and director of The Mackool Eye Institute and Laser Center in Queens, New York, as well as a professor at the New York Eye and Ear Infirmary and NYU Medical Center. “There are reasons the patient didn’t opt for PRK in the first place, including slow recovery, risk of haze and often discomfort,” he says. “The patient probably doesn’t want to go that route for retreatment.”

Dr. Mackool developed his own flap elevation technique that has since proven successful even for a LASIK flap created 29 years earlier. Dubbed Another example of Richard Mackool, MD, finding the LASIK flap with the “Dry and Depress” technique. Dr. Mackool reports success using this technique on flaps created as far back as 29 years prior.
the “Dry and Depress” technique, it requires nothing more than the standard tools a refractive surgeon would already have on hand, and consists of the following steps:

- With the surgeon seated superiorly at the excimer laser microscope, the patient looks upward, bringing the inferior cornea into view. At the 8 to 10 mm optical zone, the inferior cornea is gently dried with a sponge to improve the surgeon’s ability to detect areas of epithelial irregularity, depression or elevation.

- With a dry sponge, gently depress the adjacent central region of the cornea to flatten the mid–peripheral cornea and cause the corneal light reflex to shift peripherally. Dr. Mackool says this is the ‘a–ha’ moment when you then see the junction of the LASIK flap.

- A blunt spatula is run back and forth along the groove, penetrating the epithelium and Bowman’s membrane, and passed beneath the flap to continue the standard flap elevation. (A video of the procedure is available at reviewofophthalmology.com.)

“We’ve used this technique in 50 of 51 eyes (all had their original LASIK flap created by a microkeratome) that were between six months and 29 years post-LASIK. In one eye we could not penetrate the incision, so we performed PRK,” Dr. Mackool says. “Most notably, none of these patients developed epithelial ingrowth. We believe it’s because of the minimal disruption of the epithelium, similar to primary LASIK.”

Dr. Mackool advises surgeons to take their time looking for the flap. “If you don’t immediately find it down at 6 o’clock, look a little toward 7 or 8 o’clock, or 4 or 5 o’clock,” he says. “Just do a careful examination. We find it 100 percent of the time.”

Dr. Piracha’s technique for finding the flap varies. “You can mark the edge of the flap at the slit lamp—not the laser—with a 25- or 27-gauge needle,” he says. “That way, when you lift the flap, you’re not creating a corneal abrasion. Another way is with the current lasers with a slit lamp attached, and the third way is to actually press on the cornea with a Merocel sponge and the margin of the flap shows up. At that point, I take a very fine Sinskey hook and cleanly dissect it and initiate the flap. Then I’ll take a cannula or LASIK spatula and go underneath that space and open the flap. I’m very particular about initiating that because if you’re rough identifying the margin and entering the central space from the flap, you can get epithelial ingrowth and the ingrowth can be recurrent and persistent. If it keeps returning you may have to suture the flap, which I’ve done on patients with recurrent epithelial ingrowth.”

“Epithelium tends to adhere more laterally than it does vertically where it’s anchored, so the real challenge is to get those side adhesions separated.”

— Scott MacRae, MD

Dr. MacRae’s flap-lifting technique was adapted from Steve Wilson, MD, of the Cleveland Clinic. “He described this technique at one of the meetings, and showed a video where he took a platypus type forceps, made a small notch at the flap edge, and then just lifted the entire flap open,” he says. “I was somewhat shocked at how quickly he lifted it. It created a really clean separation of the epithelium at the edge of the flap with very little epithelial scrolls or epithelial defects around the edge of the flap. Prior to this, I used to just push the instrument horizontally to separate the flap edge, which caused more epithelial scrolls.”

It inspired Dr. MacRae to develop an instrument called the MacRae Flap Flipper (Storz). “I score the flap edge at the slit lamp with a Sinskey hook or the Flap Flipper,” says Dr. MacRae. “The leading edge of the Flap Flipper looks like a dandelion digger that allows me to gently lift and separate the flap while moving forward and lifting around the flap edge. Dr. Wilson was absolutely correct that lifting actually separates those horizontal or lateral adhesions of the epithelium, clearly avoiding epithelial tears.”

As all of these surgeons attest, nurturing the epithelium is critical. “Epithelium tends to adhere more laterally than it does vertically where it’s anchored, so the real challenge is to get those side adhesions separated,” says Dr. MacRae. “Dr. Wilson’s technique confirms that concept that the edges are cleaner if you tug vertically as you’re lifting rather than driving horizontally. That’s actually a key to performing retreats without having epithelial ingrowth. Sparing the epithelium and epithelial defects will dramatically reduce the rates of epithelial ingrowth in my experience. Using that technique, it’s extremely rare for me to have an epithelial ingrowth. If you do see a little tag of epithelium slip into the interface after you’ve lifted, then just gently tease it back away from the interface or from the edge of the flap and tease it peripherally away from the flap margin.”

Finally, Dr. Piracha advises the close consideration for lens exchange as an alternative to PRK and lifting the flap. “You have to look at the epithelial thickness and take an OCT and explain to the patient that if we do a surface treatment, it’s going to take a long time for vision to come back, and it might be worse for the first six months,” he says. “Then you have the argument to consider a lens replacement as opposed to surface treatment. That’s an option, especially with post-LASIK IOL calculations (Barrett True-K formula) and OCT imaging, and they have several options—monofocal lenses, multifocal lenses, EDOF lenses, the IC-8. It’s appealing because you don’t have the risk of an epithelial defect and it doesn’t take long to heal.”

DISCLOSURES

Dr. Mackool has no relevant disclosures. Dr. MacRae is the creator of the MacRae Flap Flipper. Dr. Piracha is a consultant to Johnson & Johnson Vision and Zeiss.
INDICATIONS AND USAGE
ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration
One drop of ILEVRO® 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications
ILEVRO® 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

Warnings and Precautions

• Increased Bleeding Time – With some NSAIDs, including ILEVRO® 0.3%, there exists the potential for increased bleeding time. Ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

• Delayed Healing – Topical NSAIDs, including ILEVRO® 0.3%, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

• Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including ILEVRO® 0.3%, and should be closely monitored for corneal health.

• Delayed Healing – Topical NSAIDs, including ILEVRO® 0.3%, may slow or delay healing. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events, which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

• Use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

• Contact Lens Wear – ILEVRO® 0.3% should not be administered while using contact lenses.

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

For additional information about ILEVRO®, please refer to the Brief Summary of Prescribing information on the adjacent page.
surface diseases (e.g., dry eye syndrome), rheumatoid corneal epithelial defects, diabetes mellitus, ocular NSAIDs including ILEVRO® Suspension and should be avoided. Patients with evidence of corneal epithelial breakdown or perforation. These events may be sight threatening. Topical NSAIDs should be used with caution in these patients. Post marketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

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

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

Serious and Otherwise Important Adverse Reactions
The following adverse reactions are discussed in greater detail in other sections of labeling:
- Increased Bleeding Time (Warnings and Precautions)
- Delayed Healing (Warnings and Precautions)

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects
- Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses up to 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival. Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

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

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

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

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

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

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

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

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

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

Shake Well Before Use
Patients should be instructed to shake well before each use.
The March Of Time

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

I was fortunate enough to have a wonderful vacation this summer—one of my ‘bucket list’ trips: an in-depth visit to Norway. It’s a magnificent country, with majestic mountains, waterfalls, glacier lakes, and interesting cities and towns—the whole thing. And, as one does, we took a lot of pictures of said mountains and beautiful vistas. Of course, to prove we were there, we took pictures of us standing in front of all those magnificent places, too. The whole nine yards. Very cliché, but somewhat expected.

I had the opportunity on the long flight back home to review them in order to see what I wanted to keep, delete, print and share. And in so many of them there was this gray-haired, wrinkled, squinty-eyed old man photobombing my pictures! I had hoped I would see that dapper, handsome, bon vivant I was used to seeing but somehow that was not to be. Someone must have stolen that portrait I had hidden in the attic, as I now hardly recognized myself. It’s curious that looking at myself in the bathroom mirror every morning wasn’t warning enough: There was something about the static image of the photo that was particularly surprising and jarring at the same time—and a bit depressing.

It’s not that I’m afraid of growing older, or of my mortality. Nor do I feel that much older. OK, I guess I do feel somewhat more sedentary, but I’ve been blaming that on the pandemic and the interruption of my previous routines. And yes, I make noises when I get up from sitting down, but I didn’t have the self-awareness of how both my physical appearance or my engagement with life have changed. At one point in this somewhat energetic trip, I must have demurred to going on another hike or something and got told to “Stop acting like an 85-year-old.” That was a shock. My response of course was that I was “just practicing.” However, as I thought about it, it’s not as far away as it should have sounded. And acting it is definitely worse than actually being it, at any age.

I do like to think that I’ve dealt with my ongoing ‘maturation’ pretty well, but really, who thinks of themselves as getting old? I imagine that most people have an awareness in their head of a version of themselves many decades younger. We don’t really see what we see; that person in the mirror is just poor lighting. I mean who really embraces feeling old? And if you don’t feel old, why should you look old? I know that’s very vain and superficial, but hey there’s a lot of money to be made addressing this insecurity. It’s very unlikely that I’ll do much about it, but maybe I should start using sunscreen. I’m way too much of a baby to get filler and Botox that I’d have to repeat every few months. So, I’m left to internalizing that slightly unsettling vision of myself as the current me. It’s inevitable.

It could be worse: I still do really think though that feeling and acting older is the sin, not the wrapper it comes in.
Dry eye affects millions of patients, and clinicians need to understand the signs and symptoms of the disease in order to help mitigate dry eye’s effects. Dry eye is difficult to define, which leads clinicians to categorize the disease as mild, moderate and severe for most cases. But there’s always underlying factors that go unrecognized which lead to ineffective treatment options for dry eye. “The key to dry-eye treatment is early identification, early intervention and prevention as much as possible,” says Christopher Starr, MD, an ophthalmologist at Weill Cornell Medicine in New York and a global ambassador for the Tear Film and Ocular Surface Society.

This article will examine various treatment options to help clinicians manage DED after identifying all signs and symptoms.

The Roots of Dry Eye
“Dry eye is an umbrella term. It includes different symptoms and signs all of which can be driven by various contributors,” says Anat Galor, MD, MSPH, an ophthalmologist at the University of Miami Health System in Florida.

The eye is affected everyday by many factors contributing to dry eye, which make it more difficult to define DED. Initially, dry eye was defined as a disorder, instead of a disease, that lead to tear deficiency and tear evaporation, but this definition failed to describe any specific pathophysiologic basis.1 In the TFOS DEWS report, society members defined dry eye as a disease for the first time, but many clinicians interpreted this definition as primarily diagnostic criteria.2 The current TFOS definition for DED was described in the DEWS II report. It states that “Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”1

“There has to be a balance of all the key components of the ocular surface, the tear film and various mechanisms, from sensation and corneal nerves to the brain with the trigeminal and the lacrimal functional unit of all the lacrimal glands and the accessory lacrimal glands, to the meibomian glands and the goblet cells,” says Dr. Starr. “All of these things need to be in tight homeostasis regulation.”

At-Home Treatments
“No matter what’s causing symptoms, there are a few things individuals can do on their own before they seek care,” continues Dr. Galor. “These include buying tear supplements, marketed under the term artificial tears, that have various viscosities and different compounds.”

Over recent years, many preservative-free eye drops began making their way on the market. Each eye drop is a unique solution with different properties to help treat various symptoms of DED. “I don’t think there’s a right artificial tear supplement; it’s more what works for the person,” Dr. Starr says.

Andrew Beers
ASSOCIATE EDITOR

Dr. Starr is a consultant for Allergan, Bausch + Lomb, Kala Pharmaceuticals, Novartis Pharmaceuticals and Oyster Point Pharma and has been affiliated with the Bausch + Lomb medical education program. Dr. Galor is a consultant for Novaliq, Novartis Pharmaceuticals, AstraZeneca, Dompé, Tarus, Bausch + Lomb, and Allergan. Dr. Akpek is a consultant for Dompé, HanAll, Iolyx, Kyria, Novaliq, Singl and Xequel and has received research support from Novartis Pharmaceuticals and Ocular Therapeutics.
Serum Tears Made Simple.

Think serum tears are hard to get?
Learn how Vital Tears has simplified the process.

At Vital Tears, our mission is to make serum tears easily available and affordable for your patients. We’ve done that for patients across the country through our:

- Rapid serum drop delivery
- Convenient blood draw options
- Affordable payment options
- Superior customer service

OR CALL TOLL-FREE (800) 360-9592

SCAN THIS CODE TO DOWNLOAD OUR PHYSICIAN INFORMATION PACKET
Feature  DED TREATMENTS

for an individual person, finding the right composition and viscosity that improves symptoms and doesn’t blur vision,” says Dr. Galor. “The more viscous the artificial tear, the more likely it is to blur vision temporarily. We try to steer people away from preservatives like BAK that can have adverse effects on nerves and epithelial cells, but there are lots of great products out there for people to try.”

While artificial tears are useful, they aren’t always the best solution for all cases. “If a patient is having to use these eye drops eight times a day or more, they’d better switch to a gel form or ointment,” says Esen Akpek, MD, an ophthalmologist at Johns Hopkins Sjögren’s Center in Maryland. “We have the impression that instilling too many eye drops could be harmful to the ocular surface by washing the mucin and oil components of the tear film.”

Other ways to treat mild dry-eye cases include home remedies that are simple for patients to include in their daily regimen. “Warming up the eyelids is a tried-and-true over-the-counter maintenance therapy, and there are many ways of doing that from run-of-the-mill washcloths under warm water to microwaving potatoes and putting them in socks to tea bags,” says Dr. Starr. “There are more sophisticated methods. For instance, the Bruder company has something call the Bruder Moist Heat Eye Compress, which is a reusable, microwavable mask.”

“Another thing people can do on their own is recognize that symptoms and signs of dry eye can be driven by environmental contributors, so it’s important to consider the environment around you,” says Dr. Galor. “Optimizing temperature and humidity, maintaining a clean environment as much as you can by changing your air filter, addressing sources of mold and installing an air purifier are all ways to improve your indoor environment.”

One environment that many patients neglect to recognize as a contributing factor is the office space. Strenuous activity in front of a screen for a long period of time eventually leads to DED complications. “Being on the computer for 12 hours a day affects your blink rate, which can affect your tear metrics,” says Dr. Galor. “People talk about the 20/20/20 rule: Set a timer, stand up, and blink a few times. Take breaks and consider the work environment. For example, installing a humidifier if your work area is arid may help your eyes feel better.” The 20/20/20 rule suggests that patients suffering from DED should set a timer for 20 minutes during computer use. Then, after the timer goes off, they should stand for 20 seconds staring and blinking at an object 20 feet away. This helps reduce screen time and encourages an increase in blink rate.

**Antibiotics and Anti-Inflammatories**

“If a patient has physician-measured clinical signs consistent with dry eye, such as decreased tear production as measured with Schirmer’s, ocular surface damage, evidenced by lissamine green or fluorescein staining, or increased osmolality, then I definitely go on to the next step, which is

---

**TABLE 1. SOME TEAR REPLACEMENT THERAPIES**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>iVizia</td>
<td>Similasan</td>
<td>A preservative-free artificial tear with sodium hyaluronate, polymers and trehalose. Available in multidose bottles. Lubricant eye gel available in single-dose vials.</td>
</tr>
<tr>
<td>Clear Eyes Pure Relief</td>
<td>Prestige Consumer Healthcare</td>
<td>A preservative-free artificial tear formulated with glycerin and sodium hyaluronate. Available in multidose bottles.</td>
</tr>
<tr>
<td>Optase Dry Eye Intense</td>
<td>Scope</td>
<td>A preservative-free artificial tear with hyaluronic acid. The MGD Advanced Lipid-based drop is also preservative-free. Both are available in multidose bottles.</td>
</tr>
<tr>
<td>Biotrue</td>
<td>Bausch + Lomb</td>
<td>A preservative-free artificial tear with hyaluronic acid. Available in single-dose vials and multidose bottles. Safe to use with contact lenses.</td>
</tr>
<tr>
<td>Blink Triple Care</td>
<td>J&amp;J Vision</td>
<td>A hypo-osmolar viscoelastic formula that mimics human tears to restore the tear film and provide relief from dry-eye symptoms by regulating osmolarity levels.</td>
</tr>
<tr>
<td>Retain HPMC</td>
<td>Ocusoft</td>
<td>A hypromellose ophthalmic solution 0.3% that relieves dry-eye symptoms by resembling natural tears.</td>
</tr>
<tr>
<td>Freshkote</td>
<td>Eyevance</td>
<td>Supports the eye’s tear film with antimicrobials and a blend of polyvinyl alcohol 2.7% and povidone 2%, which results in high oncotic pressure on the ocular surface to draw excess water from epithelial cells. Preservative-free.</td>
</tr>
<tr>
<td>Systane Hydration</td>
<td>Alcon</td>
<td>A preservative-free artificial tear formulated for sensitive eyes with HydroBoost. Available in multidose bottles.</td>
</tr>
<tr>
<td>Soothe XP Emollient</td>
<td>Bausch + Lomb</td>
<td>Restores the lipid layers with mineral oils to seal in moisture and protect against irritation.</td>
</tr>
<tr>
<td>Refresh Optive Mega-3</td>
<td>Allergan</td>
<td>Restores the lipid layer with a natural oil blend and relieves MGD symptoms. Includes carboxymethylcellulose sodium 0.5%, glycerin 1% and polysorbate 80 0.5%. Preservative-free.</td>
</tr>
<tr>
<td>Refresh Celluvisc</td>
<td>Allergan</td>
<td>A preservative-free artificial tear gel that contains carboxymethylcellulose sodium 1%.</td>
</tr>
<tr>
<td>TheraTears</td>
<td>TheraTears</td>
<td>A hypertonic, electrolyte-balanced formula that replicates healthy tears.</td>
</tr>
</tbody>
</table>
prescription eye drops,” says Dr. Akpek. “It’s important to choose the eye drop according to the clinical finding. We need to differentiate aqueous-deficient from evaporative dry eye.”

In the past, corticosteroids have been used off-label to treat inflammation in dry-eye patients. “I have a very low threshold for steroid use for inflamed eyes,” says Dr. Starr. “There’s now an FDA approved steroid for dry-eye disease flares, Eysuvis.”

Eysuvis (loteprednol etabonate 0.25%, Kala Pharmaceuticals), Lotemax (loteprednol etabonate 0.5%, Bausch + Lomb) and Flarex (FML (fluorometholone acetate 0.1%, Eyevance) in rapidly relieving the symptoms and signs of moderate or severe dry-eye disease.

“There’s now an FDA approved steroid for inflamed eyes,” says Dr. Starr. “I have been used off-label to treat inflammation in dry-eye patients. “I have been used off-label to treat inflammation in dry-eye patients. ”

“Anti-inflammatories, like cyclosporine products and lifitegrast, are generally used as a first-line therapy in people who have an immune component to their dry eye, such as Sjogren’s, graft-versus-host disease and other autoimmune diseases,” adds Dr. Galor. “But, of course, there are no absolutes and there are a lot of crossovers, so people with autoimmune dry eye also get MGD, and they often get prescribed antibiotics. People who have ocular surface inflammation, without a known autoimmune disease, often get a trial of an anti-inflammatory medication.”

Other ways to reduce inflammation in dry-eye patients is by treating with antibiotics. “A lot of the antibiotics that we use in the realm of ocular surface disease actually have some anti-inflammatory properties, and that’s where doxycycline, minocycline and azithromycin—both topical and oral—have antibiotic properties which can certainly help when there’s bacteria that are sensitive to those antibiotics,” says Dr. Starr. “They can help debulk the bacterial load, the lid margin and the ocular surface, and can play a role in everything from bacterial conjunctivitis to things like MGD and anterior blepharitis. Their anti-inflammatory properties are beneficial in the ocular surface diseases where inflammation is the core mechanism and pathophysiology.”

A novel approach to reducing inflammation and increasing tear production is Oyster Point’s Tyrvaya (varenicline). “It’s a secretagogue that is applied to the nasal mucosa,” says Dr. Akpek. “Tyrvaya could be a good replacement for over-the-counter drops because it stimulates the natural tears and doesn’t upset tear-film homeostasis through drop instillation.”

Dr. Starr adds that “this neuro-stimulation nasal spray for dry eye very likely reduces inflammation with long-term treatment.”

**Treating MGD and Blepharitis**

“MGD can present itself in several ways,” says Dr. Galor. “Some patients present with plugging and/or keratinization of the gland openings, others with thick, toothpaste-like meibum or gland dropout. Over-the-counter approaches to MGD including heating masks along with eyelid hygiene. There are several products available over the counter for this purpose.

“There are also a lot of office-based procedures that target different aspects of MGD,” Dr. Galor continues. “When people have intact glands but poor meibum quality, a procedure

### TABLE 2. SOME OPTIONS FOR TREATING INFLAMMATION, PROMOTING TEAR PRODUCTION AND/OR RESTORING THE OCULAR SURFACE

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrvaya</td>
<td>Oyster Point</td>
<td>A prescription varenicline solution nasal spray that stimulates the trigeminal nerve to naturally increase tear production.</td>
</tr>
<tr>
<td>Restasis</td>
<td>Allergan</td>
<td>A prescription ophthalmic emulsion (cyclosporine 0.05%) that increases the eye’s natural ability to produce tears and reduces inflammation.</td>
</tr>
<tr>
<td>Generic cyclosporine ophthalmic emulsion 0.05%</td>
<td>Mylan Pharmaceuticals</td>
<td>A Restasis generic (cyclosporine ophthalmic emulsion 0.05%), available in single-use vials.</td>
</tr>
<tr>
<td>Cequa</td>
<td>Sun Ophthalmics</td>
<td>A cyclosporine ophthalmic solution 0.09%; this prescription drop increases tear production using nanomicellar technology.</td>
</tr>
<tr>
<td>Xidra</td>
<td>Novartis</td>
<td>A prescription drop (lifitegrast ophthalmic solution 5%) that targets the source of dry-eye inflammation.</td>
</tr>
<tr>
<td>Lotemax</td>
<td>Bausch + Lomb</td>
<td>A loteprednol etabonate ophthalmic suspension 0.5% often used off-label for treating dry eye.</td>
</tr>
<tr>
<td>Invextys</td>
<td>Kala Pharmaceuticals</td>
<td>A loteprednol etabonate ophthalmic suspension 1% with mucus-barrier penetration technology, often used off-label for treating dry eye.</td>
</tr>
<tr>
<td>Eysuvis</td>
<td>Kala Pharmaceuticals</td>
<td>A loteprednol etabonate ophthalmic suspension 0.25% with mucus-barrier penetration technology for dry eye.</td>
</tr>
<tr>
<td>Klarity-L Drops</td>
<td>ImprimisRx</td>
<td>A preservative-free loteprednol-chondroitin 0.5% ophthalmic suspension for controlling acute inflammation.</td>
</tr>
<tr>
<td>Klarity-C Drops</td>
<td>ImprimisRx</td>
<td>A preservative-free cyclosporine ophthalmic emulsion 0.1%.</td>
</tr>
<tr>
<td>Oxervate</td>
<td>Dompé</td>
<td>A cenegefin-bkjiq ophthalmic solution 0.02% (recombinant human nerve growth factor) for treating neurothropic keratitis.</td>
</tr>
<tr>
<td>iTear100</td>
<td>Olympic Ophthalmics</td>
<td>A handheld, noninvasive neurostimulator that stimulates the trigeminal nerve to increase tear production.</td>
</tr>
<tr>
<td>Vevye</td>
<td>Novaliq</td>
<td>A cyclosporine ophthalmic solution 0.1% indicated for the treatment of inflammation and other symptoms of dry-eye disease.</td>
</tr>
</tbody>
</table>
Not an actual patient.

When Selecting a Prescription Dry Eye Treatment

**DON'T MAKE HER WAIT.**

Not an actual patient.

**Indication**

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

**Important Safety Information**

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
Xiidra® (lifitegrast ophthalmic solution) 5%

**CHOOSE XIIDRA**
Because lasting symptom relief can start as early as 2 WEEKS**

Access to Xiidra is better than ever2

**Xiidra reduced symptoms of eye dryness at 2 weeks (based on Eye Dryness Score compared to vehicle) in 2 out of 4 studies, with improvements observed at 6 and 12 weeks in all 4 studies.**1†

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Important Product Information on adjacent page.

1Pivotal trial data
The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0-100).1

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.1

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.1


XIIDRA, the XIIDRA logo and ii are registered trademarks of Novartis AG.

© 2023 Novartis 1/23 259207
XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

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

4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see Adverse Reactions (6.2)].

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [see Contraindications (4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

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

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported [see Contraindications (4)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures.

Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear [see Clinical Pharmacology (12.3) in the full prescribing information].

Data
Animal Data
Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19.

A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low [see Clinical Pharmacology (12.3) in the full prescribing information]. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

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

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

Distributed by:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936
T2020-87
**Feature: DED TREATMENTS**

that heats and/or massages the lids can be used. Some of the clinically available devices include LipiFlow [J&J Vision], Systane iLux2 [Alcon] and TearCare [SightSciences], to name a few.”

“Some people have keratinization and/or obstruction of their meibomian glands, and in this situation eyelid probing can be considered,” says Dr. Galor. “For this procedure, a small probe is introduced into the meibomian gland opening to try to relieve the obstruction.” For example, Maskin MGI probes (Katena) along with a jojoba anesthetic ointment containing 8% lidocaine releases periductal fibroses from meibomian glands, freeing glands from strictures that block the flow of indispensable meibum.3

“IPL, or intense pulse light, is gaining traction, and there’s growing evidence that it can help treat some forms of blepharitis and MGD with intense pulses of light, often in patients with rosacea and ocular lid margin disease,” says Dr. Starr. Products such as OptiLight (Lumenis) and LacryStim IPL (Quantel Medical) use wavelengths of light to stimulate the meibomian glands to facilitate the secretion of meibum, along with other beneficial mechanisms.

“Blepharitis is tied to dry-eye disease because it has an impact on

### TABLE 3. A SAMPLE OF TREATMENTS FOR BLEPHARITIS & MEIBOMIAN GLAND DYSFUNCTION

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>For Blepharitis &amp; Lid Hygiene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BlephEx</td>
<td>BlephEx</td>
<td>A painless, in-office device that helps maintain and clean the eyelid margins. Removes bacteria, biofilm and bacterial toxins. Replacement tips available.</td>
</tr>
<tr>
<td>NuLids</td>
<td>NuSight Medical</td>
<td>An at-home treatment for dry eye and lid hygiene. An oscillating tip stimulates the meibomian glands and cleans away debris.</td>
</tr>
<tr>
<td>Ocusoft Lid Scrub</td>
<td>Ocusoft</td>
<td>Contains a non-irritating formula that removes dirt, oil, debris and pollen from the eyelids.</td>
</tr>
<tr>
<td>Sterilid</td>
<td>TheraTears</td>
<td>An eyelid cleanser for removing external irritants from lids and lashes.</td>
</tr>
<tr>
<td>Avenova</td>
<td>NovaBay Pharmaceuticals</td>
<td>A hypochlorous acid wash 0.01% for long-term hygiene management of blepharitis. Kills a broad spectrum of bacteria.</td>
</tr>
<tr>
<td>Cliradex</td>
<td>BioTissue</td>
<td>A tea-tree-oil-based cleanser that relieves symptoms associated with Demodex, blepharitis, MGD, rosacea, dry eye, chalazion and other lid margin diseases. Comes in towelettes and light foam. Preservative-free.</td>
</tr>
<tr>
<td>I-Lid ‘N Lash Pro</td>
<td>I-MED Pharma</td>
<td>A professional-use hydrating cleansing gel with 20% tea tree oil for removing ocular debris and intensive cleaning of the lids and lashes. Available in a 50-mL metered dose pump.</td>
</tr>
<tr>
<td>Xdemvy</td>
<td>Tarsus</td>
<td>A lattisan ophthalmic solution 0.25% indicated for the treatment of Demodex blepharitis.</td>
</tr>
<tr>
<td>TheraPearl Eye Mask</td>
<td>Bausch + Lomb</td>
<td>A hot-and-cold therapy that helps to alleviate dry eye.</td>
</tr>
<tr>
<td>For Meibomian Gland Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LipiFlow</td>
<td>J&amp;J Vision</td>
<td>A vector thermal pulsation system for treating MGD in the office. Delivers therapeutic pulsation energies to meibomian glands to liquify and evacuate meibum.</td>
</tr>
<tr>
<td>Systane iLux2</td>
<td>Alcon</td>
<td>A handheld, portable device that targets the meibomian glands with light-based heat and compression under direct visualization in less than 12 minutes.</td>
</tr>
<tr>
<td>TearCare</td>
<td>SightSciences</td>
<td>An open-eye, blink-associated device suite that delivers consistent thermal energy to the lid structure.</td>
</tr>
<tr>
<td>MiBo ThermoFlo</td>
<td>MiBo Medical Group</td>
<td>Treats dry eye by delivering consistent, emissive heat and ocular massage to the meibomian glands.</td>
</tr>
<tr>
<td>eyeXpress</td>
<td>Holbar Medical Products</td>
<td>An eye hydration system for in-office therapy. A goggle system delivers uniform, regulated heat to the lid structure.</td>
</tr>
<tr>
<td>OptiLight</td>
<td>Lumenis</td>
<td>An intense pulsed light system for MGD indicated for professional use in patients 22 or older with moderate to severe DED and with Fitzpatrick skin types I-IV.</td>
</tr>
<tr>
<td>LacryStim IPL</td>
<td>Quantel Medical</td>
<td>Intense pulsed light system that uses a unique wavelength spectrum and train of pulses to stimulate the lacrimal and meibomian glands, reduce inflammation and improve tear film quality.</td>
</tr>
<tr>
<td>Epi-C PLUS</td>
<td>Expansione Group</td>
<td>A no-gel IPL with low-level laser therapy approved for dermatological use in the U.S. For ophthalmic use, white and yellow masks stimulate lymphatics and increase drainage. Wavelength: 633 ±10 nm; emission power: 100 mW per cm².</td>
</tr>
<tr>
<td>Thermal 1-Touch</td>
<td>Ocusoft</td>
<td>A localized heat therapy that applies heat and gentle pressure to the lids to release meibum.</td>
</tr>
<tr>
<td>Meibo</td>
<td>Bausch + Lomb; Novaliq</td>
<td>A perfluorohexyloctane ophthalmic solution indicated for the treatment of signs and symptoms associated with meibomian gland dysfunction.</td>
</tr>
</tbody>
</table>
the meibomian glands,” says Dr. Starr. “If there’s blepharitis, I want to know if it’s anterior, posterior or both; if it’s due to bacteria, to Demodex, to medications, to hormones, or to a whole host of things, because that helps me to guide my treatment.”

Depending on whether the blepharitis is anterior, posterior or mixed, the treatment options may differ. “When people have anterior blepharitis, removing the debris on the eyelashes with BlephEx is an option,” says Dr. Galor. BlephEx is a microblepharoexfoliation device that removes bacteria and toxins from the eyelids. For posterior treatments, Cliradex (BioTissue), containing 4-terpineol, a compound found in tea tree oil, cleanses the eyelid, ridding the surface of Demodex. Additionally, practitioners now have access to Xdemvy (lotilaner ophthalmic solution 0.25%), the first FDA-approved treatment for Demodex blepharitis.

“When you start talking about parasitic mites that live in your eyelids and crawl out onto your eyelid margin and deposit eggs and waste products on your eyelashes, that’s really an uncomfortable conversation to have with a patient,” says Dr. Starr. “If you see the collarettes, it’s pathognomonic and you want to decrease the mite burden and population.”

**Contact Lenses**

There’s also an interplay between contact lens use and dry-eye signs and symptoms.

“Contact lens wear can affect the eye in two ways: First, we think it affects the health of the meibomian glands,” says Dr. Galor. “Patients who are long-time contact lens wearers often have meibomian gland dropout on exam. We believe that contact lens wear at least partially contributes to this finding. Second, contact lens wear can also impact corneal nerves. People who wear contact lenses for a long time sometimes lose nerve sensitivity, so they don’t respond to the environment as robustly as they should.”

Proposing daily disposable contact lenses can help reduce the risk of DED. “We find that the daily disposable contact lenses with the more modern materials tend to be the safest of all and provide the least induction of major ocular surface issues in dry eye,” says Dr. Starr. “These tend to be very well tolerated, leading to lower risks of infections and hypoxia.”

For more severe dry-eye cases, clinicians can offer more durable and advanced contact lens options. “Scleral lenses are a good option for individuals with very low tear production and corneal and conjunctival epithelial disruption,” says Dr. Galor. “Scleral lenses produce an artificial tear layer underneath the lens that protects the surface during the day. You can also put autologous serum tears in the scleral lens to give the surface extra growth factors.”

Patients should be well educated about other treatment options and the long-term effects of scleral lenses before moving forward. “They are permanent in that the patient will have to wear them for prolonged periods of time,” says Dr. Akpek. “It’s not an interim treatment. It’s sort of like a last-resort treatment, and that’s usually done after attempting to improve the tear secretion or production and then lessening the tear loss by basically blocking the tear ducts and putting the patient on the autologous tears to renew and regenerate the epithelium.”

**Autologous Serum Eye Drops**

As pointed out in the previous section, autologous serum tears can go hand-in-hand with scleral lenses, as well as other lens options. Formulating autologous serum eye drops is a process in which the cellular and liquid components of a patient’s blood are separated in a diluted saline solution.

---

**TABLE 4. SOME PUNCTAL PLUGS & SCLERAL LENS OPTIONS**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vera180</td>
<td>Lacrivera</td>
<td>Synthetic, absorbable lacrimal plugs (poly-p-dioxanone) designed to provide temporary occlusion for approximately 180 days. Available in sizes of 0.2 to 0.5 mm.</td>
</tr>
<tr>
<td>Soft Plug Extended Duration</td>
<td>Oasis Medical</td>
<td>A short-term plug (less than three months). Available in sizes of 0.2 to 0.5 mm. Also available: absorbable collagen and permanent intracanalicular plugs.</td>
</tr>
<tr>
<td>PROSE</td>
<td>BostonSight</td>
<td>A gas-permeable prosthetic device that reduces dry-eye symptoms of pain and light sensitivity and supports ocular surface healing.</td>
</tr>
<tr>
<td>DigiForm</td>
<td>TruForm Optics &amp; Contamac</td>
<td>A scleral lens made of material with a low wetting angle to alleviate dry-eye symptoms, corneal distortion and surface irregularities. Also available in Optimum Extra and Optimum Extreme.</td>
</tr>
<tr>
<td>Onefit</td>
<td>Blanchard Contact Lenses</td>
<td>A scleral lens to help alleviate end-of-day dryness symptoms and intolerance of environmental effects with soft lenses. Provides a thin fluid cushion over the eye.</td>
</tr>
<tr>
<td>Boston IV</td>
<td>Bausch + Lomb</td>
<td>A rigid, gas-permeable contact lens with a non-stick surface that resists dirt and debris. B+L says it’s an economical choice for vision correction and dry eye. Other options such as the Boston X02, X0, EO and ES have B+L’s Tangible Hydra-PEG coating technology, which B+L says increases surface water retention and lubricity and minimizes deposits on the lens.</td>
</tr>
</tbody>
</table>

---

**Feature DED TREATMENTS**
which contains biological nutrients that are similarly present in tears. For me, the autologous serum drops are generally reserved for the more advanced, higher-severity-level ocular surface and dry-eye disease patients,” says Dr. Starr. “Because one will try traditional treatments first from over-the-counter products to FDA-approved prescription medications, punctal plugs, procedural treatments, and so on. It’s in patients with more severe disease—these are generally cases with autoimmune disease, chemical burns and chronic cicatrizening issues—that’s not necessarily amenable to multiple traditional treatments.”

Dr. Akpek elaborates further on how to use these eye drops. “In those patients who don’t respond to, for example, bandage contact lenses, punctal plugs or trying to improve the corneal epithelium, autologous serum tears with a concentration from 20 to 100 percent, four-to-six times a day, could be used,” says Dr. Akpek. “In order to enhance corneal epithelium regeneration, I do frequently employ autologous serum eye drops, whether the dry eye is aqueous deficient or evaporative.”

The key to dry-eye treatment is early identification, early intervention and prevention as much as possible.

— Christopher Starr, MD

Recent FDA Approvals
There have been recent FDA approvals as well. Miebo (Bausch + Lomb; Novaliq) Vevye (Novaliq) and Xdemvy (Tarsus) are the latest treatments to receive approval in 2023.

Miebo (perfluorohexyloctane ophthalmic solution, Bausch + Lomb), originally NOV03, is a prescription eye drop for DED that directly targets tear evaporation, especially in cases with MGD. Miebo underwent two Phase III studies, GOBI and MOJAVE. According to the clinical studies, Miebo met both its primary sign and symptom efficacy endpoints. The two primary endpoints studied were the change from baseline at week eight in total corneal fluorescein staining (tCFS) and eye dryness Visual Analog Scale (VAS) score. Researchers reported that Miebo patients experienced relief from their symptoms as early as day 15 with statistically significant reductions in VAS eye dryness scores. There was also a significant reduction in tCFS at day 15 as observed in both studies. The most common adverse reactions patients experienced were blurred vision (1.3 percent, GOBI; 3 percent, MOJAVE) and eye redness (1 percent, GOBI; 3 percent, MOJAVE).

Vevye (cyclosporine 0.1%, Novaliq), (Continued on p. 56)
How the Experts Diagnose Dry Eye

Grading the severity of dry eye by assessing signs and symptoms helps ophthalmologists treat and follow dry-eye patients.

The evaluation and diagnosis of dry eye is challenging. It’s a multifactorial condition, and reported symptoms aren’t always consistent with ocular surface changes. Generally, diagnosis of dry-eye disease entails patient history and slit-lamp examination, with additional testing performed as needed.

According to Stephen Pflugfelder, MD, who’s in practice at Baylor College of Medicine in Houston, it’s important to evaluate both signs and symptoms. “A patient could be a grade 4 from symptoms alone but not really have any signs, or he or she could be a grade 4 with signs but have no symptoms. In either case, treatment should be tailored to the severity, and it will determine how aggressive you want to be and what your options for therapy will be,” he says.

Patient Symptoms

Christopher J. Rapuano, MD, who’s in practice at Wills Eye Hospital in Philadelphia, recommends starting with a history and asking about patient symptoms. “Certain symptoms go more along with dry eye than with other conditions,” he says. “The first is the time of day when the patient is experiencing symptoms. Dry-eye symptoms tend to be worse toward the end of the day or during or after concentrated visual tasks, such as reading, computer work, watching screens and driving. Environment is also important. Do patients work in an air-conditioned office or where a fan is blowing on them? Is it a cold, dry day? Those things clue me in to the diagnosis of dry eye. The severity of the symptoms typically goes along with the severity of the dry eye.”

He adds that the importance of the patient’s history can’t be overemphasized. “I think that we miss a lot if we’re not listening to the patient’s symptoms,” Dr. Rapuano says. “Some of those will really help us determine whether it’s more dry eye, whether it’s more blepharitis, and whether it has a neurotrophic component to it. We also need to find out whether the patient has a history of herpes or diabetes.

Many diabetic patients have ocular surface issues, and it may be related to some of the neurotrophic aspects of their long-term diabetes.”

When assessing symptoms, Dr. Pflugfelder explains that there’s no universal questionnaire, but that many ophthalmologists have their own questionnaires. “The ones that seem to be used the most are the Allergan OSDI and visual analog scales, like the Symptom Assessment in Dry Eye (SANDE),” he says. “DEWS grades symptoms on a scale from 1 to 4. Symptoms include discomfort, severity...
OCULUS Keratograph® 5M
with Crystal TEAR Report:
All relevant information at a glance!

Dry eye management has never been this easy. The Crystal TEAR Report helps you perform comprehensive screenings, using the measuring results as a basis for diagnosing dry eye syndrome. The workflow is optimized for time saving and patient friendliness. All results are documented and summarized for you and your patient in a neat and easily understandable printout.

Toll free 888-519-5375    ads@oculususa.com  www.oculususa.com
and frequency, and these are two questions on the SANDE questionnaire. The first one is to grade the severity of dry eye, basically from 0 to 100, and then the frequency is the second question. In grade 1, it would be mild or episodic, occurring under environmental stress, and that would range all the way to grade 4 with severe and disabling and constant symptoms, so that would probably be 100 on the questionnaire.”

Studies have shown the OSDI and the SANDE questionnaires are equally effective. In one study, data collected from the SANDE questionnaire showed a significant correlation and negligible score differences with those from the OSDI, suggesting that the SANDE visual analog scale-based questionnaire has the potential to provide clinicians with a short, quick and reliable measure for dry-eye symptoms.1

The study included 114 patients with dry-eye disease. All patients were administered the OSDI and SANDE questionnaires at baseline and follow-up visits. The correlations between both questionnaires’ scores were evaluated using the Spearman coefficient, and their clinical differences were assessed using Bland–Altman analysis. At the baseline visit, the OSDI and SANDE questionnaire scores significantly correlated. Additionally, a significant correlation was found between changes in the OSDI and SANDE scores from baseline to follow-up visits.

**Signs**

Dr. Rapuano notes that slit-lamp findings are crucial for grading dry eye. “Fluorescein stain is important. The more fluorescein staining there is, the less healthy the ocular surface and the worse the dry eye,” he says. “And, I’ll often do lissamine green staining of the cornea, but especially of the conjunctiva. That’s important to me because some patients who have a lot of symptoms have a great-looking cornea with no fluorescein staining, but they have tons of lissamine green staining of the conjunctiva, and that goes along with dry eye. Before we were performing consistent lissamine green staining, we were missing a lot of these patients.”

Here’s what Dr. Rapuano does with his patients: “I often perform a Schirmer’s test and a Schallamach test on patients he is seeing for the first time. “I often don’t repeat it unless I need to, but it can be very helpful when evaluating first-time dry-eye patients,” Dr. Rapuano adds. “It’s helpful if it’s above 15 or below 5. In the 5 to 15 range, it’s often not super helpful, but the highs and the lows give me some idea of tear production. If it’s high, I’m thinking maybe it’s really not dry eye. If it’s really low, I’m thinking there’s definitely some aqueous deficiency going on here.”

According to Dr. Pflugfelder, another criterion is visual changes, which can range from nothing to constant and possibly disabling. “There could also be a decrease in the patient’s actual visual acuity. The next item is conjunctival injection, ranging from none or mild to 2+,” Dr. Pflugfelder says. “Again, there are schemes to grade injection, like the Waterloo scale. Conjunctival staining can range from none to marked, and corneal staining can range from none to severe punctate and confluent staining. DEWS criteria grade corneal signs from none to grade 4, which would be filamentary keratitis, mucus clumping, adherent debris or corneal ulceration. Then, we evaluate lids and meibomian glands.

Grade 1 would mean meibomian gland disease is variably present, and grade 3 would be that it’s definitely present and moderate to severe. The next item is fluorescein tear breakup time. Grade 1 would be variable, and grade 4 would be immediate breakup. The last criterion is the Schirmer test score, which would range from normal tear production to the most severe aqueous deficiency, which is less than 2 mm. Again, the problem is that the DEWS scale doesn’t weight any of these. There is no composite score, so it’s really a gestalt. I use the scale to grade clinical severity, and if the patient has any of the criteria for grade 3 or 4, that’s how I would grade it. It doesn’t have to be all of them, but they do usually go together.”

He adds that he doesn’t like the grading systems, but his preference is for the one from the first DEWS study. “It combines signs and symptoms. However, it could be flawed because we don’t know how to weight the signs and symptoms,” Dr. Pflugfelder explains. “Some of the dry-eye patients we see objectively don’t look like they have severe dry eye. Rapid tear breakup time may be the only sign, but their symptoms could be off the charts. Other patients who have severe autoimmune dry eye, like Sjögren’s syndrome, may have very minimal symptoms, but their corneas look horrible and they can’t see well. Right now, I’m just not aware of anything that would distinguish between those groups, but the DEWS at least includes both. I’ve been using a stepwise grading scheme from 1 to 4 if either the symptoms or the signs are bad.”

Dr. Rapuano adds that classifying dry eye is important both for determining treatment and for following patients after they’ve begun treatment. “I’ll usually call it mild, moderate, severe, or very severe,” he says. “As it gets more severe, I’m much more aggressive with my treatment. The more severe the dry eye is, the more frequently I’m following them, and I’ll increase the regimen more quickly.”
The ingredients of Oasis TEARS VISION® were carefully chosen to develop this patent pending formulation and support optimal visual health.

Oasis TEARS VISION®

- Addresses age-related vision changes associated with oxidative stress and inflammation
- Supports dietary supplementation for general eye health through antioxidant and anti-inflammatory compounds

Learn more with our NEW White Papers

Nourishing and sustaining the eye-care community—for the long term.

View and Download the White Papers

Learn More
Call (844) 820-8940
Email customerservice@oasismedical.com
Visit www.oasismedical.com

© 2023 OASIS Medical, Inc. Oasis TEARS® name and logos are registered trademarks of OASIS Medical Inc.

He explains that mild dry-eye patients may be seen every three to six months, while severe patients may be seen every few weeks to a month. “If it’s mild, we start a regimen with the plan to see the patient in six months. We tell him or her to come in sooner if it’s getting worse,” Dr. Rapuano says. “Whereas, if it’s a pretty severe patient, I might see him or her in a month, or if it’s a super severe patient, I might see him or her in a week or two just to make sure there’s not any corneal erosion. For the vast majority of patients, it’s one to three months, and the three-month time period is because some of our treatments, such as Restasis or Xiidra, are getting reasonably good results by the three-month time period, so if I’m starting a patient on one of those, I often want to give the full three-month course to see whether that treatment is working or not.”

Dr. Pfugfelder says you don’t need to be overwhelmed with tests to be effective. “Ophthalmologists would be doing a great job to have a symptom questionnaire and then just follow a standardized protocol for staining the cornea and the conjunctiva, looking at the meibomian glands, and assessing tear production or volume,” Dr. Pfugfelder says. “If they’re doing that, they’re doing a great job, and with those components, they can definitely grade the severity and classify it as meibomian gland disease or aqueous deficiency. If a physician is going to make dry eye a large part of his or her practice, he or she should probably develop a standardized protocol for diagnosis and grading.”

DEWS II Recommendations

The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II Diagnostic Methodology Subcommittee has recommended the following order and clinical practice procedural guidelines:


Regarding symptoms, a positive result is a DEQ-5 score of 6 or above or an OSDI score of 13 or higher.

Regarding signs, the first step is to assess tear breakup time. According to DEWS II, three measurements should be taken, with the median value recorded. For diagnostic purposes, choose the lower median breakup value of the two eyes. The cut-off for a positive finding can be as low as 2.7 seconds for automated algorithms and up to 10 seconds for subjective observation techniques.

When non-invasive techniques cannot be used, fluorescein tear breakup time can be considered. However, because it’s more invasive, osmolarity measurement should be performed first. For fluorescein tear breakup time, fluorescein should be instilled at the outer canthus to avoid ocular surface damage. For optimal results, view the eye one to three minutes after instillation. A positive finding is a breakup time less than 10 seconds. The following tips can be helpful:

• Osmolarity should be assessed with a temperature-stabilized, calibration-checked device. A positive result is 308 mOsm/L or more in either eye or an interocular difference of more than 8 mOsm/L.
• Lissamine green staining is performed to assess conjunctival and lid margin damage. Observation should occur between one and four minutes after instillation. Observation through a red filter potentially aids visualization. A positive score is more than nine conjunctival spots.

• Lid wiper epitheliopathy can be observed stained with fluorescein, rose bengal or lissamine green dyes, although there seems to be a preference for just lissamine green.

Dr. Pfugfelder says you don’t need to be overwhelmed with tests to be effective. “Ophthalmologists would be doing a great job to have a symptom questionnaire and then just follow a standardized protocol for staining the cornea and the conjunctiva, looking at the meibomian glands, and assessing tear production or volume,” Dr. Pfugfelder says. “If they’re doing that, they’re doing a great job, and with those components, they can definitely grade the severity and classify it as meibomian gland disease or aqueous deficiency. If a physician is going to make dry eye a large part of his or her practice, he or she should probably develop a standardized protocol for diagnosis and grading.”

The Future of Dry Eye

Dr. Pfugfelder says that the incidence of dry eye is on the rise. “I could see dry-eye patients 10 hours every day,” he says. “Part of it is our lifestyle and climate change. Many people work on a computer at least eight hours a day in an air-conditioned environment. There are occupational, environmental, and probably nutritional factors that are contributing to its increased prevalence. We also have an aging population.”

Dr. Rapuano agrees. “With the warming of the world, global climate change may be part of that,” he says. “Masking for the past three years was also a part of that. The air would just kind of blow up in people’s faces from the mask.”

Aesthetics are an important patient concern that can affect how they feel about themselves and around other people. Patients commonly use products and services that promise aesthetic enhancement, including lash extensions, eyelash growth treatments, colored contact lenses, eye makeup, eye creams, and serums. Increasingly, patients also seek out redness-relieving eye drops to improve the appearance of their eyes.

Ocular Redness: A Key Patient Concern

Demand is substantial: 4 in 10 sales in the over-the-counter (OTC) eye drop category are for redness relievers.\(^1\) Because ocular redness is often caused by “minor” eye irritations, patients may not recognize it as a valid concern that they can discuss with their eye care provider (ECP) and are, therefore, not always professionally counseled on which redness reliever is best for them. Without their ECP’s input, patients can sometimes lean on potentially unreliable sources, such as the store shelf, their peers, commercials, or the internet. Herein lies an opportunity to educate patients and guide them through the enormous ocular redness market while also addressing the root cause of their symptoms.

LUMIFY®: A Clinically Proven Approach to Treating Ocular Redness

LUMIFY® (brimonidine tartrate ophthalmic solution) 0.025% drops are indicated for relieving redness of the eye due to minor eye irritations. Most redness relievers are α1- or α1/α2-adrenergic receptor agonists; α1-adrenergic receptor agonism constricts corneal arterioles, hindering oxygen delivery to the cornea, which causes rebound redness. Brimonidine tartrate, by contrast, is selective for the α2-adrenergic receptor, primarily constricting ocular surface venules, which do not affect ocular surface oxygen delivery and therefore is not associated with high levels of rebound redness.\(^7\)

In 6 clinical studies with over 600 patients, low-dose brimonidine tartrate demonstrated a 1 minute onset of action, which persisted for up to 8 hours.\(^4\) It had a favorable safety profile and, consistent with its mechanism of action, a low incidence of rebound redness (1.2%).\(^4\) Adverse event rates did not significantly differ from control, and the most common adverse events in brimonidine-treated eyes were reduced visual acuity (4.0%) and conjunctival redness (2.6%).\(^3\)

Opportunity for ECPs to Step In

Market research indicates that patients report using of redness relievers an average of 3 days per week.\(^7\) Ocular redness is a key concern for many patients, but the OTC eye care market contains an often overwhelming array of products. Understanding and communicating the benefits and challenges of available products is key to helping patients narrow down which products–out of everything on the shelf–might work best for them.

LUMIFY® provides safe and effective redness relief for my patients dealing with minor eye irritations

LUMIFY® is a redness reliever drop differentiated in its mechanism of action, rapid effects, and minimal rebound redness. LUMIFY® provides patients with excellent redness relief. In recommending a product as efficacious and reliable as LUMIFY®, ECPs can establish themselves as trusted professionals who can address patients’ needs—both clinical and aesthetic. This can lead not only to improved patient outcomes and satisfaction but could also enhance trust in their relationship with their ECP.

Dr. Melissa Toyos
Practices at Toyos Clinic located in Tennessee, Mississippi, and New York

Incorporating ocular aesthetics into the patient conversation

- Ask patients if they are happy with how their eyes look and feel
- Ask patients if they use OTC eye care products and if they are satisfied with them
- Consider that the aesthetic aspect of eye care may be just as important to a patient as the clinical aspect
- Be ready and willing to provide OTC recommendations

Content © 2023 Bausch + Lomb
Catching a Red Eye

With careful examination and history-taking, most unusual causes of red eye can be uncovered.

Ophthalmologists are no strangers to the classic red eye presentation, which tends to rear its head in the clinic on a daily or weekly basis. Typical causes include conjunctivitis, subconjunctival hemorrhage, dry eye, blepharitis, topical glaucoma medications and contact lens overwear. The full list of red-eye differentials is vast, however.

Here, experts share some tips for narrowing down the cause, as well as some of the more unusual culprits behind red eye.

Patient Symptoms

Asking patients about any associated symptoms is a key step toward determining the underlying cause of red eye. “I usually ask patients if they’re having any irritation, pain, discharge, light sensitivity or foreign body sensation,” says Masako Chen, MD, an assistant professor of ophthalmology and director of Comprehensive Eye Services at New York Eye and Ear Infirmary of Mount Sinai. “If I’m suspicious for some of the more unusual causes of red eye, I might also ask certain patients about recent sun exposure or contact with sick people, topical and systemic medication use, history of past eye or other infections, and history of skin lesions or skin cancer removal.”

“If patients report symptoms such as redness, some irritation, dryness and foreign body sensation that have been occurring on and off for a long time, that makes me think of a dry-eye situation,” says Sezen Karakus, MD, an assistant professor of ophthalmology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine. “But, if they mention pain, light sensitivity, difficulty opening the eyes or decreasing vision, those are red flags that something more serious may be going on.”

A Thorough Examination

Simple symptoms can sometimes mean serious disease. Dr. Karakus says it’s very important to carry out a thorough comprehensive exam for red-eye patients. “Some of the issues causing surface diseases may affect the corneal nerves as well,” she says, “and in those cases, patients may not have significant pain or discomfort, but their vision may change.”

Here are some points to keep in mind during the exam:

- **Observe the patient.** “The exam begins the second you walk into the room and see the patient,” says Bennie H. Jeng, MD, chair of the ophthalmology department and director of the Scheie Eye Institute at Penn Medicine in Philadelphia. “In addition to the eyes themselves, look at the eyelids and the face. See what the patient’s reaction is when the lights are on. If they have photophobia, that may point you to something else. When looking at the eyelids, note their position. Is there any malposition that might be causing exposure that then causes red eye?”

- **Look with the lights on.** “Looking with the lights on is important because sometimes red eyes will appear differently under different lighting,” says Dr. Jeng. “With scleritis, for example,
the quality of the redness and inflammation is different when you look at it without the slit lamp under room lighting.

• Be methodical and consistent.
  “During the exam, go carefully from front to back,” says Dr. Chen. “Make sure there’s no scarring, blepharitis or meibomian gland disease. Look at the palpebral conjunctiva to ensure there aren’t any tumors, foreign bodies, follicles, papillae, symblepharon or other abnormalities. Examine the cornea to ensure there are no infiltrates or ulcers, and check for anterior chamber cells to rule out anterior uveitis. Depending how the exam goes, you may choose to dilate the patient for a fundus exam. I tend not to dilate patients with viral conjunctivitis to make sure I don’t infect my equipment.”

• Always flip the lids. When checking the conjunctiva, it’s important to pull the lower lid out and flip the upper eyelid to check for abnormalities such as foreign body, follicles, papillae or symblepharon. “Follicles or papillae are signs of a certain type of inflammation with allergic or infectious causes,” Dr. Karakus says. “Also check for scarring, because that could indicate more serious problems.”

  “A foreign body in the eye is an unusual cause of chronic conjunctivitis,” says Dr. Jeng. “A contact lens may be stuck in the upper fornix, or sutures may have eroded from underneath the conjunctiva.”

• Stain the eye for additional clues. “When checking for corneal and conjunctival abnormalities, we use vital dyes to identify areas with more dryness or inflammation or anything abnormal,” Dr. Karakus says. “With those vital dyes, we can see which parts of the eye are particularly affected by the disease. This could give us a clue as to whether the red eye results from underlying autoimmune disease or is a nerve-related issue, for example. It may also be toxicity from certain eyedrops or environmental exposure. If the lower part of the cornea is dry, then that might indicate a lid margin-related disease such as blepharitis or meibomian gland dysfunction.”

  “Check for abnormal color.” “If the eye isn’t a normal color or the cornea has a gray or white spot, this may indicate a more serious inflammatory cause or infection,” Dr. Karakus continues. “There may be other findings within the cornea such as edema or irregularities. From there, you’d go through the differentials.”

• Check for abnormal vasculature.
  More serious causes of red eye, including keratitis, iritis or scleritis, often present with abnormal vasculature. “Ocular surface squamous neoplasia often presents with abnormal corkscrew vessels,” adds Dr. Chen. “Dilated and large vessels may mean you need to do gonioscopy to look for tumors, masses or iris lesions.”

• Ask about “redness relief” drops. “Patients don’t like the appearance of red eye,” says Vatinee Y. Bunya, MD, MSCE, co-director of the Penn Dry Eye and Ocular Surface Center of Scheie Eye Institute in Philadelphia. “I always tell patients that there’s a danger of rebound redness if vasoconstrictors (e.g., naphazoline) are used chronically and then stopped. The eyes may appear redder than before. For special occasions, such as a wedding or a big meeting, using an anti-redness drop such as Lumify (brimonidine tartrate) is okay, but like vasoconstrictors, it shouldn’t be used long-term. It’s best to treat the root cause of the red eye, rather than mask it.”

Dr. Bunya says that it’s possible these drops could make it more difficult to tell what’s going on since the patient may feel okay and their eyes don’t look visibly red. However, “more serious causes will have signs other than a red eye,” she says. “Lumify won’t help with light sensitivity or a bad infection.”

• Bring the patient back sooner.
  If the patient history doesn’t fit the exam, don’t be afraid to rethink the diagnosis, especially if the patient isn’t getting better. “Chlamydia, for example, can cause a chronic conjunctivitis that doesn’t respond to treatment and can last several weeks,” Dr. Bunya says. “If I’m not 100-percent sure about the diagnosis, I’ll bring the patient back a bit sooner. Most times, if you see the
MANY MANIFESTATIONS OF THYROID EYE DISEASE (TED) ONE ROOT CAUSE

TEPEZZA alleviates many of the symptoms of TED. TEPEZZA has been shown to be effective in patients with TED, without concomitant steroids.

See how TEPEZZA can transform your patients' eyes.

References:
TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, dry skin, weight decreased, nail disorders, and menstrual disorders.

Information or visit TEPEZZAhcp.com for more information.
TEPEZZA
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia:

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss:

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients’ hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• Infusion Reactions [see Warnings and Precautions]
• Exacerbation of Preexisting Inflammatory Bowel Disease [see Warnings and Precautions]
• Hyperglycemia [see Warnings and Precautions]
• Hearing Impairment Including Hearing Loss [see Warnings and Precautions]

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 conditions, adverse reaction rates observed in the clinical trials compared to 4% (1 of 25 patients) approximately 23% (5 of 22 patients) of menstruating women (amenorrhea, metrorrhagia, dysmenorrhea) were reported in Table 1. In addition, menstrual disorders completed 8 infusions (89% of TEPEZZA patients and 93% of infusions) or placebo given as an intravenous infusion every (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (93% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater frequency in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TEPEZZA (N, %)</th>
<th>Placebo (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles/spines</td>
<td>13 (17%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Pain</td>
<td>14 (17%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (16%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (15%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>5 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>9 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Nail disordera</td>
<td>4 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase

Hearing impairment includes hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, hydropsyracusus, hypoaacusis, autoaphony and tinnitus).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. 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.

Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).

Nephrology: oliguric renal failure.

Gastrointestinal: colic, urgency, tenesmus or incontinence.

Hematology: anemia.

Neurology: tremor, ataxia, syncope, headache.

Ophthalmology: visual impairment.

Dermatology: rash, urticaria.

Respiratory: dyspnea, hypoxia.

Cardiovascular: hypotension.

Hepatology: jaundice.

Immunology: allergic reactions.

OVERDOSAGE

No information is available for patients who have received an overdose.

PATIENT COUNSELING INFORMATION

Embrion-Fetal Toxicity

• Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
• Advise and educate female patients of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

• Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

• Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping, colic, urgency, tenesmus or incontinence.

Hyperglycemia

• Advise patients on the risk of hyperglycemia and, if diabetic, discuss with the healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

Hearing Impairment Including Hearing Loss

• Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

 Manufactured by: Horizon Therapeutics Ireland DAC, Dublin, Ireland U.S. License No. 22282

Distributed by: Horizon Therapeutics USA, Inc. Deerfield, IL 60015 TEPEZZA and the HORIZON logo are trademarks owned by or licensed to Horizon. © 2023 Horizon Therapeutics plc L-TEP-US-00036 07/23
Chemical Burn
Among the less run-of-the-mill reasons behind red eye are chemical burns. Chemical burns often result from household cleaning agents and medications. Fortunately, Dr. Karakus says, “It’s often obvious when a chemical was involved because the patient is usually able to tell you about an incident, the type of chemical and which areas were exposed.

“Sometimes only part of the eye is affected, and other times the whole conjunctiva appears severely inflamed,” she continues. “Abrasions or ulcers of the cornea or conjunctiva may also be present. Chemical burns often cause inflammation in the limbus.”

Mild burns are usually treated with topical steroids and lubricants. If epithelial defects are present, prophylactic antibiotics may be used.

Photokeratitis
“When you see diffuse corneal staining, that’s usually an indication of some form of toxicity from something in the air, preservatives in eyedrops or even ultraviolet light,” says Dr. Karakus. “Many patients aren’t aware of the damage from UV-light exposure until they start having symptoms.”

Careful questioning about activities or recent trips can help pinpoint the cause. Dr. Karakus says UV-sterilization devices that aren’t properly covered while in use are often the culprits behind this form of keratitis, but highly reflective surfaces can also cause UV-induced keratitis. “I once had a patient who went skiing without goggles on, and the sunlight reflecting off the snow caused a diffuse keratitis,” she says.

A case of nightclub photokeratitis was described in which a 30-year-old nightclub technician reported working with intense ultraviolet lights for six hours before experiencing symptoms.¹ He had severe conjunctival injection and corneal punctate epithelial erosions, and was treated with oral analgesics, timolol, lubricant eyedrops and antibiotic prophylaxis. At one week his corneas were clear, BCVA was 20/20 (from 20/30 OD and 20/40 OS) and IOP was 12 mmHg OU.

Anterior Uveitis
“Anterior uveitis is differentiated from more common causes of red eye such as conjunctivitis by the presence of inflammation and accumulated white blood cells in the anterior chamber,”

Dr. Karakus says. “Patients often have pronounced limbal flush.”

Other signs may include keratic precipitates, hypopyon and iris nodules. Patients usually report symptoms of rapid-onset pain, redness and photophobia. A thorough medical history can provide further clues, as anterior uveitis often arises from illness, a virus or an associated underlying disease. Ankylosing spondylitis and psoriatic arthritis are risk factors. Acute anterior uveitis resolves with anti-inflammatory therapy.

Dr. Chen notes that “there was a case that was initially diagnosed as bilateral conjunctivitis, but on the anterior segment examination, there were a lot of cells, and no follicles or papillae on the eyelids. The patient was diagnosed with bilateral anterior uveitis and further bloodwork confirmed tubulointerstitial nephritis and uveitis (TINU).”

Acute Angle Closure
One of the more unusual and serious causes of a red eye is acute angle closure glaucoma, where outflow pathways are obstructed, often by ocular trauma. “Patients have acute onset of redness and sometimes light sensitivity,” says Dr. Bunya. “They may have blurred vision because the cornea is edematous from the acute rise in pressure. At the slit lamp, the anterior

---

chamber will appear narrower. Pressures will be high.

“Any time a patient has any sort of acute vision loss or severe pain, that puts them in a different category of urgency than someone who comes in with no changes in vision and little pain,” she explains.

Intraocular pressure-lowering treatment should be initiated as a first-line treatment for acute angle closure.

**Episcleritis & Scleritis**

Episcleritis and scleritis may be idiopathic or arise from associated systemic conditions, but scleritis is more frequently associated with underlying systemic disease, particularly rheumatologic conditions.

“Scleritis affects the deeper vessels and has more of a radial pattern than the articulated network that you’d normally see with either episcleritis or conjunctivitis,” says Dr. Jeng. “Both episcleritis and scleritis can be localized, in contrast with conjunctivitis which generally affects the entire conjunctiva.”

Patients with episcleritis are usually asymptomatic. “Episcleritis isn’t as disruptive a disease, so supportive therapy such as lubrication is often all that’s needed,” Dr. Jeng says. “If the patient is bothered by it, a low-dose mild steroid can sometimes work.

“Scleritis, on the other hand, requires treatment,” he continues. “I don’t generally find that topical drops are all that effective. Scleritis patients usually need to be treated systemically. First, identify and treat the underlying disease. That will usually treat the scleritis. If the patient doesn’t have an underlying disease associated with the scleritis, I’ll usually go with a nonsteroidal anti-inflammatory to treat the inflammation.”

**Herpes Simplex**

Primary herpes simplex virus ocular disease is often mistaken for conjunctivitis. It may manifest with unilateral follicular conjunctivitis. Common symptoms include eye redness, pain, light sensitivity, watery eyes and eyelid inflammation. Reactivation of the disease may be triggered by stress, sun exposure, fever or certain medications. It’s important to identify and treat herpes infections promptly with antivirals.

“Be careful about prescribing steroids to patients without seeing them,” Dr. Bunya points out. “I recently had a patient whom I followed for years for dry eye and other chronic eye problems. She called, asking if I could call in some steroid drops for what she thought was a typical flare-up, but I said, ‘It’s better if you come in so I can take a quick look.’ It turned out that she had a herpes simplex infection of the cornea. If I had prescribed steroids without seeing her, her herpes infection would have worsened.”

**OSSN**

Experts say that though it’s rare, ocular surface squamous neoplasia should remain on clinicians’ radar when evaluating red-eye patients, as OSSN may masquerade as chronic conjunctivitis.

“Ocular cancers should always be in our differential, especially if the patient isn’t responding to treatment,” Dr. Karakus says. “If there’s a lesion, you’ll usually see it either within the conjunctiva or growing over the cornea. It’s very important to check the undersides of the eyelids—flip the upper lid and look inside the lower lid. You’ll see signs such as a lesion or bumps and lumps. Sometimes there may be follicular conjunctivitis, which would make you think of a second infectious cause or some other chronic inflammation. But if the patient isn’t improving with standard treatment, always consider OSSN.”

Treatment depends on the size of the lesion and what you’re suspicious for. “For an ocular surface tumor such as a small squamous cell, we generally do an excisional biopsy with cryotherapy and take the whole thing, and then check for margins on pathology,” says Dr. Jeng. “If it’s large, an incisional biopsy can be done for diagnosis, and then it may be treated using topical chemotherapy drops. Optical coherence tomography is sometimes used to diagnose the type of tumor and treat it without getting a biopsy.”

**Conjunctivochalasis**

With decreases in collagen, older patients may experience a red-orange eye from conjunctivochalasis. “Conjunctivochalasis isn’t usually recognized early on, and patients are often given only artificial tears,” Dr. Karakus says. “The condition may also result from chronic inflammation of the eyes due to conditions such as prior thyroid eye disease, ocular rosacea, dry eye or chronic eye allergies.”

It’s important to differentiate this condition from conjunctivitis and lid malposition disorders such as floppy eyelid syndrome. “Every time the patient blinks, the loose conjunctival folds that develop cause irritation, redness and more inflammation,” she says. “Patients experience irritation, pain, discomfort and fluctuating vision problems.”

Lubricants can relieve mild symptoms, but topical corticosteroids are sometimes needed to help reduce inflammation. In some cases, approaches to tighten redundant conjunctiva are employed, such as cauteronization, conjunctival excision or scleral fixation.

“It’s worthwhile to mention that superior limbic keratoconjunctivitis will present with more pronounced redness under the upper lid in the bulbar conjunctiva,” Dr. Karakus adds. “Sometimes the conjunctiva will bunch in that area, creating friction. SLK is also associated with thyroid diseases.”

“As long as you have the differentials in your head and do a thorough anterior segment exam, you’ll get to the right diagnosis,” says Dr. Chen. “Take a really thorough history. If the history doesn’t fit with the exam, investigate further. Be methodical about the exam and go from the front to back in a consistent manner, and don’t skip any steps. Always flip the lid.”

MIEBO™ (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for the treatment of the signs and symptoms of dry eye disease.

**IMPORTANT SAFETY INFORMATION**
- MIEBO should not be administered while wearing contact lenses. Contact lenses should be removed before use and for at least 30 minutes after administration of MIEBO.
- Instruct patients to instill one drop of MIEBO into each eye four times daily.
- The safety and efficacy in pediatric patients below the age of 18 have not been established.
- The most common ocular adverse reaction was blurred vision (1% to 3% of patients reported blurred vision and conjunctival redness).

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.

Please see accompanying Brief Summary of full Prescribing Information for MIEBO.


NEW!

*Indicated for the treatment of the signs and symptoms of DED*

MIEBO is the first and only Rx eye drop for DED that directly targets evaporation.

**Inhibits tear evaporation**
- Forms a monolayer at the air-liquid interface of the tear film which can be expected to reduce evaporation.

**Rapid and sustained relief**
- Improvement in tCFS and eye dryness as early as Day 15 continued through Day 57 in 2 pivotal studies.

**Excellent tolerability**
- Low rate of burning or stinging on instillation.
- Blurred vision and conjunctival redness were reported in 1%-3% of individuals.

*The exact mechanism of action for MIEBO in DED is not known.*

**INDICATION**
MIEBO™ (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for the treatment of the signs and symptoms of dry eye disease.

**IMPORTANT SAFETY INFORMATION**
- MIEBO should not be administered while wearing contact lenses. Contact lenses should be removed before use and for at least 30 minutes after administration of MIEBO.
- Instruct patients to instill one drop of MIEBO into each eye four times daily.
- The safety and efficacy in pediatric patients below the age of 18 have not been established.
- The most common ocular adverse reaction was blurred vision (1% to 3% of patients reported blurred vision and conjunctival redness).

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.

Please see accompanying Brief Summary of full Prescribing Information for MIEBO.
Although cataract surgery is the most common surgery being performed currently, the occasional hiccup does occur. For example, a lack of capsular support presents a challenge requiring the surgeon to determine how to fixate an intraocular lens. Common reasons for loss of support include trauma, endophthalmitis or uveitis, Marfan’s syndrome and pseudoexfoliation, to name a few.1

For decades, surgeons didn’t have many options for situations where capsular support was lacking. Today, new techniques have come to the forefront and gained widespread popularity. We asked experts to discuss their preferred methods and they shared tips and pitfalls every surgeon should consider.

Capsular Tension Rings and Scleral-Sutured IOLs
Anterior chamber IOLs, which date back to the 1950s, aren’t favored by many in modern ophthalmology due to their long-term risks of bullous keratopathy and glaucoma.2,3 Historically, one of the other popular techniques was to suture a lens to the iris with a Prolene suture. “The problem with suturing the lens to the iris is that it rubs right on the back of the iris and that chafing can also cause iritis, macular edema and pigment dispersion, and therefore it can cause clogging of the trabecular meshwork and glaucoma,” says Naveen Rao, MD, who is a cornea, cataract and anterior segment surgeon practicing in Boston. “Iris suturing may initially work for many patients, but there can be some late complications of that as well, which is why many surgeons currently opt for scleral fixation instead of iris fixation.”

Scleral-sutured IOLs have long been the chosen technique of Gregory S. H. Ogawa, MD, who practices in New Mexico. Proponents of scleral-sutured lenses note that studies have shown scleral-sutured IOLs to have a better safety profile than anterior chamber IOLs or iris-fixated IOLs.1 Scleral-sutured IOLs can reduce the risks of complications because the lens is positioned farther away from anterior segment structures. One prevailing concern with scleral-sutured IOLs has been the risk of suture breakage. A retrospective case study reported 30 of 61 eyes needed two or more procedures due to a complication during or after the surgery, 17 of which were due to breakage of polypropylene sutures.4 Some of this concern has been mitigated with the introduction and use of Gore-Tex.

For his part, Dr. Ogawa partially attributes his preference of scleral-sutured IOLs to geography. “In New Mexico, some patients drive up to five hours from remote locations for surgery,” he says. “I take a one-and-done philosophy. If I try new techniques and they don’t work as well, my patients can’t easily come back to my office to remedy the issue. For me, scleral suturing is a bulletproof approach.”

Dr. Ogawa always uses a one-piece PMMA CZ70BD IOL (Alcon). Once he notices bad zonules, Dr. Ogawa uses capsule support hooks before carefully removing the cataract. He then makes a pair of scleral incisions behind the iris 2 mm apart and a 7-mm wide scleral groove. “I use a...
2L Cionni ring, which has two suturing eyelets, and put a 1.5-cm piece of Gore-Tex through the suturing eyelet that I want to use. I usually put a 5-cm piece of 10-0 nylon through the lead eyelet—not the suturing eyelet because I want to help minimize stress on the capsular bag,” says Dr. Ogawa. “I then reach through the scleral incisions with 25-ga. curved forceps to externalize those pieces of Gore-Tex CV-8 (which is the smallest currently made) and then put a two-wrap throw.”

If the zonules are bad due to pseudoxfoliation, Dr. Ogawa will suture both eyelets.

“Essentially, even if the zonules are absolutely terrible, this will support the bag,” he continues. “I place the lens implant in the bag before I remove the OVD and use a self-retaining infusion cannula at the limbus to keep things formed if need be. Then I’ll adjust the tension on the two sutures to make sure I can center things well, and then I put four single-wrap throws on both of those Gore-Tex sections. I cut the tails off the Gore-Tex and use straight tying forceps to bury the knot inside the eye. It needs to be totally inside the eye, otherwise it can erode through the conjunctiva. For this I’ll take down conjunctiva in those places and then use 10-0 vicryl to close the conjunctiva.” (Figure 1)

If a situation is particularly extreme and proves too difficult to insert a 2L ring, Dr. Ogawa will remove the capsular bag and perform an anterior vitrectomy and implant a Gore-Tex sutured IOL.

For nearly 30 years Dr. Ogawa has used this technique and the reliable, long-term results have given him no reason to adopt one of the more recently developed techniques. He estimates that he’s scleral-fixated over 2,000 IOLs, about half with Gore-Tex and the other half with polypropylene.

Although most surgeons would currently opt for smaller incisions and perhaps suture Ahmed segments with a regular CTR, Dr. Ogawa sees an advantage of a scleral tunnel with a self-sealing incision when using a 7-mm optic. “Creating that tunnel incision is something that came from the fact that I started doing eye surgery when incisions were bigger, and that might be a challenge for someone who just finished residency within the last five years and never performed a single scleral tunnel incision,” he says. “When I’m hands-on teaching this technique, we use cadaver eyes and make 15 scleral tunnels in the eye all over just to practice.”

He adds, “If speed is the most important thing, then this isn’t the technique for you. For me, the most important thing is having a good result that stands the test of time.”

Dr. Ogawa evaluated the results of 202 scleral-sutured 9-0 polypropylene posterior-chamber IOL surgeries several years ago (before the use of Gore-Tex) and the data revealed no cases of IOL tilt, suture erosion or unusual IOP elevation. Patients showed overall improvement in visual acuity, sustained IOL fixation and refractive stability and minor complications.

There are some potential risks to be cognizant of if choosing to scleral fixate, notes Dr. Rao. “The reason that a lot of surgeons don’t favor scleral-suturing is, historically, those scleral-sutured lenses were made of non-foldable PMMA plastic, which requires a big 7-mm incision. That large incision can be more of a risk, especially in older patients, including the risk of suprachoroidal hemorrhage and the requirement to use many sutures to close the incision,” he says. “There are also a variety of other strategies that can be adopted but, generally speaking, most of us don’t want to use a large incision. There are some smaller foldable lenses that can be used for scleral fixation. One of them that’s been popular with our retina colleagues is the Akreos lens, which is a foldable hydrophilic acrylic. However, hydrophilic material tends to opacify over time, especially if there

Figure 1. Scleral-suture Fixation Steps: (Top left) A scleral groove is created with a tunneling blade. (Top right) One suture arm comes over through the lead haptic’s eyelet, the other between the eyelet and optic. (Bottom left) IOL placement occurs simultaneously while the straight tying forceps hold the externalized sutures. Before closing the case, intraoperative Purkinje images confirm lens centration (bottom right).
INDICATION
IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
• IZERVAY 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 IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order 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.
NOW APPROVED

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

To learn more and stay up to date, visit IZERVAYecp.com

• Neovascular AMD
  • In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

• Increase in Intraocular Pressure
  • Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

• Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

Copyright ©2023 IVERIC bio, Inc., An Astellas Company. All rights reserved.
US-AP-2300095 09/23
IZERVAY™ (avacincaptad pegol intravitreal solution)  
Rx only  
Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.  

1 INDICATIONS AND USAGE  
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).  

2 DOSAGE AND ADMINISTRATION  
2.1 General Dosing Information  
IZERVAY must be administered by a qualified physician.  

2.2 Recommended Dosage  
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.  

2.4 Injection Procedure  
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed. Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP. The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbiocide should be given prior to the injection. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel. Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay. Any unused medication product or waste material should be disposed of in accordance with local regulations.  

3 DOSAGE FORMS AND STRENGTHS  
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.  

4 CONTRAINDICATIONS  
4.1 Ocular or Periocular Infections  
IZERVAY is contraindicated in patients with ocular or periocular infections.  

4.2 Active Intraocular Inflammation  
IZERVAY is contraindicated in patients with active intraocular inflammation.  

5 WARNINGS AND PRECAUTIONS  
5.1 Endophthalmitis and Retinal Detachments  
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.  

5.2 Neovascular AMD  
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.  

5.3 Increase in Intraocular Pressure  
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.  

6 ADVERSE REACTIONS  
The following potentially serious adverse reactions are described elsewhere in the labeling:  

- Ocular and periocular infections  
- Active intraocular inflammation  
- Neovascular AMD  
- Endophthalmitis and retinal detachments  

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

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham. Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.  

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye  

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>IZERVAY</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased IOP</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Choroidal neovascularization</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Blurred Vision*</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS  
8.1 Pregnancy  
Risk Summary  
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits. Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.  

Animal Data  
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rabbits received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC). An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.  

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

8.3 Pediatric Use  
Safety and effectiveness of IZERVAY in pediatric patients have not been established.  

8.5 Geriatric Use  
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.  

17 PATIENT COUNSELING INFORMATION  
Advises patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.  

Manufactured by:  
IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054  
are subsequent procedures that involve the use of gas or air inside the eye—and several retinal surgeries require gas and air, and several corneal procedures, such as endothelial keratoplasty, require gas and air, and that can cause opacification of this lens that’s now been sutured.”

Samuel Masket, MD, who is a founding partner of Advanced Vision Care, and clinical professor at the Stein Eye Institute, UCLA, advocates use of the femtosecond laser, capsule support hooks and in-the-bag devices such as a capsular tension ring, Ahmed segments (CTS) and/or modified capsular tension rings (Cionni, Malyugin). “Once the capsular bag is emptied the degree of zonulopathy is assessed and appropriate capsule support devices implanted,” he says. “I also advocate careful cleaning of the anterior subcapsular lens epithelial cells in all cases at surgery to prevent fibrosis and phimosis of the anterior capsulotomy. Depending on the degree of zonulopathy, it might be necessary to perform a pars plana vitrectomy.”

Dr. Masket was presented with a 54-year-old female patient who had sustained a bungee cord injury to the left eye that resulted in a cataract with significant zonulopathy and anterior vitreous prolapse. “At surgery a triamcinolone-assisted bimanual anterior vitrectomy was performed followed by cataract removal aided by capsule support hooks (MST),” he says (Figure 2). “Subsequently, a CTR was placed in the capsule bag and an Ahmed segment sutured to the sclera inferotemporally. During OVD removal vitreous was noted to prolapse through the main incision, necessitating pars plana vitrectomy. Five years later, the IOL capsular bag complex was noted to be stable and centered and there’s no evidence of anterior capsule phimosis.”

Figure 2. Samuel Masket, MD, demonstrates the use of MST capsule support hooks to aid in the removal of a cataract before placing a capsular tension ring.

Intracocular Lens Fixation Techniques

“There’s no doubt that intrascleral haptic fixation is the current method of choice for most surgeons,” says Dr. Masket. “These procedures generally take less time and require smaller incision sizes than scleral suturing methods with large PMMA IOLs.”

Intrascleral haptic fixation builds on the sutureless technique developed by Gabor Scharioth, MD, in 2006. The Scharioth technique fixates a three-piece IOL in the ciliary sulcus and the haptics in a limbus-parallel scleral tunnel or pocket. Burying the haptics reduces risks of conjunctival erosion, chronic inflammation and recurrent bleeding.

About one year later, the first glued PC IOL implantation was done by Amar Agarwal, MD, of Chennai, India. In a “glued” IOL technique, a scleral flap covers the part of the externalized haptic and seals it with fibrin glue.

The technique begins with corneal marking 180-degrees opposite each other for the creation of two 2.5-mm scleral flaps, followed by conjunctival peritomy and wet cautery of the cornea at the corneal marks. Two straight sclerotomies are made 1 mm from the limbus under the existing scleral...
The scleral flaps and conjunctiva are sealed with 10-0 vicryl sutures or fibrin glue. Then suturing of the corneal incision by a vitrectomy at the sclerotomy site, tucked inside a scleral tunnel, followed by a vitrectomy at the sclerotomy site and grasp the leading haptic to pull it through after the IOL has unfolded. Dr. Agarwal recommends an assistant hold this haptic tip in the middle, the haptic has a risk of breaking. Catching it on the tip allows you to transfer the haptic from one set of forceps to another.

Dr. Agarwal points out that the “handshake” technique—when the second haptic flexes into the anterior chamber and is grabbed by the other set of glued forceps—is an essential component of its success (Figure 3). “You’re transferring the haptic from one hand to the other until you catch it on the tip,” Dr. Agarwal explains. “Imagine if you grabbed it in the middle, the haptic has a risk of breaking. Catching it on the tip allows it to come out easily and clearly.” (A video of this procedure is available at reviewofophthalmology.com.) Since developing this technique, this is the only one he uses for IOL fixation. In 2020, he published a retrospective case series to assess the results and complications of “glued” IOLs >5-12 years postop. Clinically, no tilt was seen in 87 of 91 eyes and no sub-scleral haptic was visible in 50 percent of them. The highest complication was glaucoma (7.6 percent), IOL luxation (4.4 percent) and macular edema (4.3 percent). In another separate study of 50 patients (25 with sutured IOLs and 25 with glued), more complications were encountered in the suture-fixation group (56 percent) vs. glued (28 percent) (p=0.045).

Dr. Agarwal offers a few examples of candidates for the glued IOL technique. “Take a patient with a micro cornea, about 8 mm. If I put a normal 12.5-mm IOL in the bag of an 8-mm eye, the lens will never have space to open,” he says. “In this case we would use the glued IOL technique with an 8 mm IOL, but the haptics are outside, meaning the optic is 6 mm.

“If a patient has a large eye, we perform a small iridotomy in the area where the sclerotomy will bring me, coming out 1 to 2 mm from the limbus,” he continues. “I bring it out 0.5 mm from the limbus so I’m more anterior, and the more haptic I’m externalizing, the more haptic I’m tucking into the Scharioth pocket. And that is why those patients do very well.”

Dr. Agarwal says patients are very happy with this technique and reports he even performed it on his own 85-year-old mother-in-law.

The technique has become popular in the field, and Dr. Rao says it’s successful. “However, it does require a conjunctival peritomy,” he says. “Taking down the conjunctiva is a little bit time consuming and requires some scleral and conjunctival dissection. So, that has its downsides as well. There’s a little more time required because you have to then close the conjunctiva and close the scleral flaps that are made. That would be the only downside of that, although it’s a great technique.”

Dr. Masket has had complications related to the glued technique referred to him, including an extruding haptic three years postop. “With the glued IOL technique, the haptic scleral tunnel must be well constructed and of appropriate and uniform depth,” he notes.

Approximately 10 years after the glued IOL technique was introduced, Shin Yamane, MD, introduced the “flange” technique, in which the IOL haptics are cauterized at a low temperature, creating a flange that is buried in the sclera, obviating the need for sutures or tunnels. “The ‘flange’ method has also been adapted to malpositioned IOLs, employing large-bore Prolene suture material,” says Dr. Masket.

Recognized and referred to as the “Yamane” technique, it involves two bent needles. A three-piece IOL is inserted into the anterior chamber with the trailing haptic externalized. Using a thin-walled 30-ga. needle, an angled sclerotomy is made through the conjunctiva 90 degrees from the lens incision, 2 mm posterior to the limbus. As it enters the sulcus, the needle goes toward the leading haptic, which is threaded through it with intracocular forceps. Another sclerotomy is made.
180 degrees from the first, again with a 30-ga. thin-walled needle, through which the trailing haptic is threaded (Figure 4). After confirming centration of the lens, both haptics are externalized into the conjunctiva and then heated with low-temperature cautery to create a 0.3-mm flange. The flanges are tuck through the conjunctiva and into the scleral tunnels.

“The reason the Yamane technique is so popular is because it’s very elegant,” says Dr. Rao. “It doesn’t require any conjunctival or scleral dissection. All that’s needed is the little tracks that get created in the sclera with two 30-ga. thin-walled needles. And the nice thing about it is it’s quick, it’s much less invasive and it’s compatible with a very stable lens position. Many of us have switched over to that as our primary mode of fixation when there’s no capsular support.”

Dr. Rao says the most common complication would be a decentered or tilted lens. “Once the lens has been placed in the eye and surgery is over, it’s hard to go back in there and recenter that lens—usually that means we have to take out that lens and put in another one,” he says. “There are other risks, such as the potential to inadvertently pass the needle through the ciliary body, or if you’re not careful you could inadvertently pass the needle into the retina. I haven’t seen that complication, but that would be one concern that some surgeons have with needles that are passing in and out of the eye. Normally, we prefer to use blunt tip cannulas in the eye rather than needles. This is a unique surgery where we’re actually passing a needle inside the eye.”

“I’ve seen complications with the Yamane technique,” says Dr. Masket. “Among the concerns is that the intrascleral needle passages are ‘blind’ but need to be symmetrical and exactly 180 degrees apart in order to prevent decentration, tilt and optic capture. Perhaps using ‘on-board’ OCT can help guide the needle passes for more accurate placement.”

Dr. Rao agrees and admits the Yamane technique comes with a significant learning curve. “It’s not totally straightforward, especially for people who are doing their first few cases,” he says. “It can be quite tricky to know how to pass the needle through the sclera in such a way that the lens sits totally symmetrically and it has to be centered and it shouldn’t have any tilt to it. So there’s some difficulty there in judging the angle that the needles are tunneled through the sclera. It has to be very symmetrical. There are some tricks to do it but certainly, for the first five to 10 cases there’s a significant learning curve. Some surgeons have attempted it and then felt like it didn’t work, and it’s usually because of an asymmetry of the angle of the needle trajectories through the sclera.”

He recommends practicing at labs and on model eyes. “At most meetings, there are labs to learn this,” Dr. Rao notes. “There’s a wonderful eye model for the Yamane technique made by SimuEye, called Iris Suturing and IOL Fixation. We use this model in the AAO intrascleral haptic fixation lab, for which I’m course director. It’s a much better model honestly than any surgeons learning this technique. Most people are learning the Yamane technique, so unless someone has glued IOL training or has seen enough videos to know what to do if this happens, they may have some difficulty there. In the AAO lab for glued IOL and Yamane techniques, I like to stress to learn both, not just Yamane. I think it’s really important.”

As an instructor and surgeon adept in the Yamane technique, Dr. Rao offers some important pearls for success.

• “Always use a thin-walled, 30-ga. needle and it has to be from the manufacturer TSK, which is in Japan,” he says. “No other 30-ga. needles will work; no other thin-walled needles will work. There are other manufacturers that say they have thin-walled 30-ga. needles and I would just urge any surgeons learning this technique not to trust it—it must be the one made by TSK.”

• The preferred lens for Yamane is the Zeiss CT Lucia 602 lens. “There are some surgeons who have tried...
Feature IOL FIXATION TECHNIQUES

the Yamane technique with other lenses such as the Johnson & Johnson Vision AR40 or ZA9003, but I really would encourage anyone starting with this technique to start with the Zeiss CT Lucia 602 lens, which has much more resilient haptics that are made of PVDF,” Dr. Rao says. “I have no financial interest in that or at any of these products. It’s just much more versatile for this technique. The haptics of that lens can be manipulated much more than any other three-piece lens with less risk of damage to the lens.”

*Consider involving retina colleagues. “It’s really important when there’s a dislocated IOL to do pars plana vitrectomy or when there’s any complex cataract surgery and the surgeon thinks there may be any lenticular fragments that fall into the vitreous,” he says. “Those really should be cleaned out with a pars plana vitrectomy in combination with a retinal surgeon in many cases, because otherwise those lens particles can cause chronic cystoid macular edema.”

“If you’re going to be going in there for the Yamane technique, try to do this in conjunction with a retinal surgeon so that a full pars plana vitrectomy can be done,” continues Dr. Rao. “I also encourage most surgeons to create a peripheral iridotomy, because sometimes with the Yamane technique, the iris can backbow post-operatively, and plaster itself against the IOL and it can cause chafing. To relieve this reverse pupillary block it’s good if surgeons create a peripheral iridotomy in any clock hour of the iris.”

DED Treatments

Originally CyxdlASol, is a prescription eye drop for the treatment of signs and symptoms of DED. According to clinical trials, Vevye’s safety and efficacy was assessed in a total of 1,369 patients with dry-eye disease, of which 738 received Vevye. The primary endpoint was the percentage of patients achieving ≥10-mm improvement from baseline in Schirmer’s Tear Test score. In the CYS-002 study, 8 percent of 51 Vevye patients achieved this endpoint at 29 days as opposed to 0 percent in the placebo group (n=51). In the CYS-004 study, 11 percent of 409 Vevye patients achieved this endpoint at 29 days as opposed to 7 percent of the 395–patient placebo group. The most common adverse effects Vevye patients experienced were instillation–site reactions (8 percent) and temporary decrease in visual acuity (3 percent).

Xdemy (lotilaner 0.25%, Tarsus), originally TP-03, is a prescription eye drop for the treatment of Demodex blepharitis. According to clinical trials, efficacy was demonstrated by a significant improvement in the reduction of collarettes by day 43, with some patients seeing improvement as early as two weeks. The endpoints in two Phase III studies, SATURN-1 and SATURN-2 (n=833), observed mite eradication and erythema cure. Out of 833 patients, 415 received Xdemy for treatment and 418 received a placebo.

In the SATURN-1 trial, 81 percent of Xdemy patients had a collette grade of 0 or 1 (range 0 to 4, where Grade 0 indicates ≤2 collarettes on the eyelid and Grade 4 indicates ≥two-thirds of the eyelid has collarettes) on day 43 as opposed to 23 percent in the placebo group. In the SATURN-2, 89 percent of Xdemy patients had similar results to those in the treatment arm of SATURN-1 as opposed to 33 percent in the placebo group.

By day 15, the SATURN-1 trial reported 68 percent of Xdemy patients achieved complete mite eradication. The most common adverse reactions patients experienced were instillation site stinging and burning (10 percent), and more severe reactions experienced were chalazion and punctate keratitis (2 percent).

“When looking under a slit lamp you’ll see the collarettes, especially in somebody who has symptoms of dry eye or recurrent itchy, scaly lid margins,” says Dr. Starr. “This can be treated with the approved drop. I’m sure there’s going to be a lot of after-market studies looking at things like adjuncts that might make Xdemy more effective and work faster.”


Managing Steroid-Induced Glaucoma

This secondary glaucoma has a unique pathophysiology that may inform treatment approaches.

DOUGLAS J. RHEE, MD
CLEVELAND

Nearly 30 to 40 percent of all normal adults, and almost all primary open-angle glaucoma patients are steroid responders, demonstrating clinically significant elevated intraocular pressures following corticosteroid use. It’s important to intervene early in the course of steroid-induced glaucoma to prevent irreversible optic neuropathy and vision loss. This condition can be tricky to treat in patients who require continued steroid therapy for underlying conditions.

Though it’s considered a form of open-angle glaucoma, steroid-induced glaucoma has a different pathophysiology from primary open-angle glaucoma.

Here, I’ll discuss why these two diseases may require different management approaches.

Risk Factors for a Steroid Response

Key risk factors for a steroid response include high myopia, type 1 diabetes mellitus, connective tissue disorders (e.g., rheumatoid arthritis), pigment dispersion, traumatic angle recession, primary open-angle glaucoma, prior penetrating keratoplasty, the duration of steroid therapy and the steroid’s anti-inflammatory potency.

Age is also a risk factor. Children have a strong intraocular pressure response to topical steroids, and younger patients (under 10 years old) are at the greatest risk for steroid-induced glaucoma. This glaucoma subtype accounts for about a quarter of all acquired glaucoma in children.

Route of Administration

As a general rule of thumb, the closer to the center of the eye the steroid is administered, the greater the risk. So, for example, steroid response risk is very low with intra-articular joint and intranasal administration and increases with inhaled, oral, intravenous, topical, periocular and intraocular administration.

A meta-analysis on intranasal corticosteroids (484 studies with 10 RCT) reported a relative risk of 2.24 (95% CI, 0.68 to 7.34 percent) compared with placebo. The absolute increase in incidence of elevated intraocular pressure was 0.8 percent (95% CI, 0 to 1.6 percent) compared with placebo in non-glaucomatous individuals—a risk of less than 1 percent.

A single case report described elevated intraocular pressure with inhaled steroids in a young child.

The risk with systemic administration of steroids varies, but it’s been reported to be low, ranging from less than 1 percent to 10 percent.

About 3 to 4 percent of patients treated with topical difluprednate experience a significant IOP increase >10 mmHg above baseline to 21 mmHg or more. Steroid-induced IOP responses after corneal transplantation are also well documented. Steroids are readily absorbed by the thin skin of the eyelids and around the eyes—anecdotally, many ophthalmologists have heard of a physician self-treating with a steroid face cream who comes in with pressures of 40 mmHg and massive vision loss.

The sub-Tenon’s route has a significantly high risk, likely due to its proximity to the anterior chamber angle. A multicenter study of individuals treated with cortisone for uveitis demonstrated a 35-percent incidence of IOP elevation >24 mmHg.

For intravitreal administration, there’s a reported 12- to 15-percent risk of a >10-mmHg IOP rise after Ozurdex (dexamethasone), and an up to 50-percent risk with intravitreal triamcinolone acetonide.

Two Unique Pathophysiologies

Though they share a mechanism of increased aqueous outflow resistance, steroid-induced glaucoma and primary open-angle glaucoma aren’t the same disease. Unlike primary open-angle glaucoma, steroid-induced glaucoma typically resolves spontaneously once steroids are discontinued. Based on their respective pathophysiologies, different approaches to treatment may be
The risk for steroid-induced glaucoma is partially influenced by the site of administration. In general, the closer to the center of the eye, the greater the risk. The steroid's anti-inflammatory potency and the duration of steroid therapy also play a role.

- **Primary open-angle glaucoma.** The mechanism of primary open-angle glaucoma involves an increase of transforming growth factor beta-2 (TGFB2), which causes dysregulation of the extracellular matrix within the juxtacanalicular trabecular meshwork.
  
  Another probable mechanism of this glaucoma subtype may be decreased trabecular meshwork cellularity. However, this mechanism has been observed only in cadaver eyes that were medically treated and/or had previously undergone surgery, not in untreated trabecular meshwork tissue. So, it's unclear whether decreased cellularity was the result of the disease itself or its treatment. Another challenge with this theory is that the rate of cell loss to be greater in glaucomatous eyes.

- **Steroid-induced glaucoma.** One way steroids increase resistance to outflow by inducing dysregulation of the actin cytoskeleton (cross-linked actin networks [CLANs]). CLANs cause endothelial cellular stiffness and subsequently trigger an IOP increase. This has been observed within trabecular meshwork cells in cell cultures, cadaveric organ perfusion and in live mice. Very limited evidence suggests CLAN formation may also play a role in primary open-angle glaucoma pathophysiology, but the mechanism hasn't been observed in untreated trabecular meshwork tissue.
  
  In addition to CLAN formation, steroid-induced glaucoma involves dysregulation of the extracellular matrix, but this dysregulation is markedly different from that of primary open-angle glaucoma when seen on electron microscopy. Steroid-induced glaucoma exhibits more extracellular matrix accumulation in the juxtacanalicular region, as well as increases in curly collagen 6 and inhibition of matrix metalloproteinase enzymes from increasing levels of TIMPs. Additionally, a buildup of fine fibrillar material resembling fingerprints occurs, along with collagen IV, heparin sulfate, fibronectin, and an increase in other matrix proteins such as decorin, myocilin, fibrillin and secreted frizzle-related protein.

**Medical Management**

Discontinue steroids first, if possible. If the patient has been on steroid therapy for more than 18 months, IOP elevation may last for several weeks. Topical steroids can be switched to a lower potency. Then, start a prostaglandin analog—either topical or sustained release bimatoprost.

I recommend trying a rho kinase inhibitor sooner, rather than following the usual stepping pattern after a prostaglandin analog to the medications that decrease aqueous, because the rho kinase inhibitor mechanism of action potentially targets the pathophysiology of steroid-induced glaucoma.

Rho kinase inhibitors affect the actin cytoskeleton by disrupting the actin stress fibers and focal adhesions in trabecular meshwork cells. In a steroid-induced OHT mouse model study published earlier this year (n=56), morphological changes (extracellular matrix accumulation) and reduced trabecular meshwork effective filtration area induced by dexamethasone were partially reversed after one week of treatment with a rho kinase inhibitor (p<0.05) or five-week discontinuation of dexamethasone (p<0.01). This correlated with reduced IOP. IOP reductions were greater in rho kinase inhibitor-treated eyes than eyes that discontinued dexamethasone treatment.

Prostaglandin analogs should remain the first-line treatment.
however, because they impact MMPs and TIMPs, targeting another part of steroid-induced glaucoma’s pathophysiology. These drugs shift the MMP/TIMP balance in the ciliary body and the trabecular meshwork toward greater turnover of extracellular matrix.22-29

Selective Laser Trabeculoplasty

It’s unclear whether there are any meaningful differences between primary open-angle glaucoma and steroid-induced glaucoma with regard to SLT success. A retrospective study reported a 72-percent SLT success rate (±20 percent reduction from baseline IOP) in 25 eyes with steroid-induced glaucoma.30

Another retrospective study (n=608 eyes) reported that steroid-induced glaucoma patients did better with SLT than primary open-angle (p=0.005) or pseudoxfoliation (p=0.01) glaucoma patients, but a significantly higher baseline IOP for steroid-induced glaucoma eyes may have been a confounder.31

In the same study, the two-year failure rate for steroid-induced glaucoma patients was 54-percent failure, compared with 84 percent (p=0.01) for pseudoxfoliation glaucoma and 84 percent for primary open-angle glaucoma (p=0.005).

Surgical Management

There’s a paucity of literature specifically comparing the efficacy of our incisional surgical procedures in POAG versus steroid-induced glaucoma.

• Goniotomy. A retrospective study of steroid-induced glaucoma versus primary open-angle glaucoma using Trabectome found no difference in the survival curve.32 A greater IOP response was seen in the steroid-induced eyes, but they also had a much higher baseline IOP—a problem with retrospective cohort comparisons.

The incidence of steroid response after either Trabectome or iStent goniotomy is about 12 percent.33 Greater axial length, low-tension glaucoma and traumatic glaucoma were risk factors for steroid response after goniotomy. In eyes with axial length >25 mm, the incidence was 40 percent.

• GATT. A retrospective chart review of 13 patients demonstrated that GATT was effective for steroid-induced glaucoma,34 which isn’t surprising. GATT resulted in a significant IOP reduction at all post visit, with all patients experiencing IOP reduction >20 percent at two years. The number of glaucoma medications also decreased significantly from preoperatively to 0.8 medications at the last follow-up.

The rho kinase inhibitor mechanism of action potentially targets the pathophysiology of steroid-induced glaucoma.

Another retrospective chart review of 46 eyes reported that GATT was effective for short-duration steroid-induced glaucoma.35 IOP decreased from mean 30.8 ±8.3 mmHg at baseline to 11.2 ±2.6 mmHg after one to two years (n=28). At the final follow-up, 45 eyes had IOP <21 mmHg and 39 eyes had IOP <18 mmHg with or without medication. Steroid response wasn’t seen in any eyes after surgery. A few other case reports have reported GATT efficacy.36-37

In conclusion, SLT and incisional procedures have comparable efficacies in steroid-induced glaucoma and primary open-angle glaucoma. Anecdotally, I’ve observed that trabeculotomies do better if the depot steroid remains in the eye. For medical management, I recommend using a prostaglandin analog as a first-line agent because these drugs alter the MMP/TIMP balance and can reduce the buildup of extracellular matrix. Consider using a rho kinase inhibitor as a second-line agent after the prostaglandin analog because this drug class directly affects CLANs.  

Support the Education of Future Healthcare & Eyecare Professionals

THE RICK BAY FOUNDATION for Excellence in Eyecare Education

Scholarships are awarded to advance the education of students in both Optometry and Ophthalmology, and are chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

INTERESTED IN BEING A PARTNER WITH US?

www.rickbayfoundation.org

(Contributions are tax-deductible in accordance with section 170 of the Internal Revenue Code.)

ABOUT RICK
Rick Bay served as the publisher of The Review Group for more than 20 years. To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty. To those in the industry and the professionals he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

THE RICK BAY FOUNDATION for Excellence in Eyecare Education

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

GLAUCOMA MANAGEMENT | Steroid-induced Glaucoma


ABOUT THE AUTHOR
Dr. Rhee is a professor and chair of the Department of Ophthalmology and Visual Sciences at Case Western Reserve University School of Medicine. He is also the director of the Eye Institute, University Hospitals of Cleveland. He receives research funding from Allergan/Abbvie, Glaukos, iVantis/Alcon, Cleveland Eye Bank Foundation and Ocular Therapeutics. He is also an ad hoc consultant for Alcon, Allergan, Avellino and Iantrek.
An Update on Fundus Autofluorescence

This imaging method can help elucidate retinal disease, monitor progression and possibly advance therapy.

Autofluorescence is a natural phenomenon by which a fluorophore is excited by a certain wavelength of light, causing it to re-emit this light at a longer wavelength. It’s also a powerful tool for monitoring endogenous fluorophores and biological conditions. Fundus autofluorescence is an in vivo imaging tool that enables non-invasive metabolic mapping of natural and pathological fluorophores in the posterior pole, mainly the retina and retinal pigment epithelium.

In this review, we highlight some recent developments in FAF imaging that have enhanced our understanding of retinal diseases and have promising prospects for monitoring disease progression, following patients in clinical trials and potentially influencing treatment outcomes.

Autofluorescence Explained

There’s a relationship between the morphofunctional properties of the fluorophores and their emission feature. Each fluorophore has a particular AF signature. There’s probably a continuum of the spectral fundus autofluorescence from blue to near-infrared (NIR) because of the combination of the different fluorophores (for example melanolipofuscin granules of different orders). FAF must be interpreted depending on the wavelength used, as different wavelengths will excite different fluorophores. The fluorescent spectrum can therefore allow for topographical mapping of the endogenous fluorophores like lipofuscin, melanin or melanolipofuscin at the level of (post mitotic) retinal pigment epithelium/photoreceptor (outer segment) complex.

Schepens Eye Research Institute’s Francis Charles Delori, PhD, and his colleagues first noticed in vivo FAF during vitreous fluorophotometry. Several types of light sources can be used to stimulate the fundus to exhibit autofluorescence. Flood illumination projects a single flashlight to the entire retina, but pre-retinal structures can impede the AF signals. A study by New York retinal specialist Richard Spaide suggested shifting the emission and excitation wavelengths to the red end of the spectrum to resolve the impeding signals from pre-retinal structures. Other teams proposed the use of filters of longer wavelengths (excitation filter: 535 to 580 nm; barrier filter: 615 to 715 nm) that operate with excitation in the green spectrum and emission in the yellow-orange spectrum and are also.

Figure 1. Blue Autofluorescence. Normal autofluorescence (A), dry AMD (B) (adapted from Ly et al13) and Stargardt’s disease (C) (adapted from Jeffery et al14). Copyright license for Fig. 1, B and C: http://creativecommons.org/licenses/by-nc/4.0/. Images have not been modified from original publication.
called green-AF. The most used and most efficient type of light source is therefore a laser (with a fixed unique wavelength) through the use of confocal scanning laser ophthalmoscopy, which helps overcome AF signals from preretinal structures like the lens, and has the best signal-to-noise ratio and retinal safety. To date, the commercially available cSLOs allow for exploration of FAF at 488 nm (blue) and 787 nm (NIR). The RPE/retina complex is known to be autofluorescent both with blue excitation and at near-infrared autofluorescence, and have a different pattern, due to the selective excitation of different fluorophores by each wavelength.

**Blue Autofluorescence**

Low-powered laser beams are used in cSLO, with excitation filters (488 nm) and emission filters (500 to 580 nm) which are used to detect AF signals and are also called short wavelength (SW) AF or blue AF. Blue AF was the first clinically used AF as a diagnosis tool, after the use of blue excitation light for fluorescein angiography. The blue AF comes from the outer segment of the photoreceptors and the RPE due to the formation and accumulation of lipofuscin. An irreversible non-enzymatic reaction of retinaldehyde with lipid (phosphatidylethanolamine) in photoreceptor outer segments, results in formation of lipofuscin/bisretinoid fluorophores, which can be excited by blue light, emitting a green light. The bisretinoids of lipofuscin are a family of 20 compounds, of which A2E is the best-known fluorophore. These accumulate in the lysosomal storage bodies from photo-oxidative alterations, and its conjugate double bonds promote light absorption and fluorescence emission. The emission spectra of the fundus shift slightly to shorter wavelengths in healthy subjects and even more in patients with age-related macular degeneration, likely reflecting the accumulation of lipofuscin in the RPE/retina with aging and in AMD.

High concentration of xanthophylls (lutein and zeaxanthin) and melanin result in hypoAF of the foveal region because of a masking effect. Lack of RPE in the optic disc and blocking of AF by the blood contents in the retinal vessels result in the dark appearance of both optic disc and vessels on AF (Fig. 1A). Less evident blockage by macular pigments and less signal reduction over the optic disc and retinal vessels are noted on green-AF (fundus camera). HypoAF signal is noted in conditions with reduced RPE cell number, masking or lower concentration of lipofuscin. RPE atrophy (such as in atrophic AMD, Figure 1B), fibrosis, presence of intraretinal fluid, pigment or blood accumulation are all causes for hypoAF. HyperAF signals are often noted in conditions with increased lipofuscin (such as Stargardt’s disease [see Figure 1C], Best’s and other types of dystrophies).

**Near-Infrared (NIR) Autofluorescence**

This is an in-vivo imaging technique that uses excitation at 787 nm and emission (>830 nm) beyond the red end of the visible spectrum. The fluorophores examined by NIR-AF are melanin and melanolipofuscin, with a major contribution from RPE, and a smaller contribution from the choroid. The antioxidant properties of melanin are believed to have a protective effect on the eye with AMD. Melanin helps delay the accumulation of lipofuscin in the retina and choroid. In healthy eyes and contrary to blue AF, the NIR-AF signal is maximal in the foveal area, which has a horizontal width of 8.8 degrees. This is due to a larger concentration of RPE cells in the foveal area, and no absorption of emitted NIR-AF signal by macular pigments (See Figure 2A). Some studies suggest that melanin becomes AF in NIR following oxidization, with an increase of NIR-AF signal in aging patients and at the border of atrophic lesions in AMD patients (Figure 2B).
Find qualified ophthalmic technicians fast

Finding a qualified ophthalmic technician for your practice can be difficult. That’s why private practices and large employers alike trust Eyes On Eyecare® for specialized job posting and recruiting services.

SOURCE TALENT MORE EFFICIENTLY WITH OUR:

- Large talent pool of active and passive job seekers
- Syndication to major job platforms and cross-promotion to our affiliate network
- Dedicated recruiting team with years of eyecare experience sourcing talent for specialized positions

“I had such a wonderful experience using Eyes On Eyecare. It was so easy to post a job and they walk you through the entire process. I recommend them to everyone I know.”
- Ashley Wojcik

Learn more at eyesoneyecare.com/hire-now
While blue AF requires a strong blue illumination, NIR-AF uses a laser source above 750 nm, which is a faint red light, well-tolerated by patients. This allows the potential of longer imaging times (~30 seconds) with adapted set-ups, mainly adaptive optics SLO (AOSLO), to characterize RPE at a cellular scale using their NIR-AF potential.21–23

Short wavelength (SW)-AF and NIR-AF have complementary roles in evaluation of lipofuscin and melanin, and their role in AMD pathogenesis. SW-AF failed to detect geographic atrophy in 24 percent of the eyes with GA. With the introduction of Syfovre (pegcetacoplan, Apellis) and Izervay (avacincaptad pegol), C5 complement inhibitors for arresting GA progression, NIR-AF seems to have more promise. The use of AF in these clinical trials plays an important role, and thus missing 24 percent of GA would have a significant impact on these trials and outcomes.24,25 NIR-AF helps detect changes earlier than SW-AF in patients with GA. The fovea appears hypoAF in blue AF due to macular xanthophyll pigments absorbing the blue light, whereas on NIR-AF, the fovea is brighter than the parafoveal region due to increased melanin content and a lack of NIR filtering by macular xanthophylls. Hence, SW-AF may overestimate GA in the foveal area and underestimate it in the extrafoveal area. Therefore, some suggest to use NIR-AF in conjunction with SW-AF for monitoring patients with GA.24,26

Interestingly, in ABCA4 diseases (with elevated lipofuscin levels), lipofuscin fluorophores are noted to contribute to NIR-AF signals and are thought to be melanolipofuscin-associated fluorophores (See Figure 2C).10,11,14

**Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO)**

FLIO is a relatively novel imaging tool that’s gained interest in the ophthalmic community and has shown promise in diagnosis and monitoring of various retinal disorders. Fluorescence lifetime imaging has been used in vivo for cancer diagnosis and skin evaluation. It’s used by the Heidelberg Spectralis system and has been shown to provide additional information when compared to traditional imaging techniques. Essentially, it measures the

Figure 3. Quantitative autofluorescence. A: Different patterns used to measure qAF to different precision degree (adapted from Kleefeld et al.)31 B: Example from different patients treated with hydroxychloroquine (HCQ) at different doses (adapted from Reichel et al).32 Copyright license for Figs. 3A and B: http://creativecommons.org/licenses/by-nc/4.0/. Images have not been modified from original publication.
AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- A Message from Review's Chief Medical Editor: Here We Go Again
- Differentiating Diagnosed and Undiagnosed PACG and OAG: Find out which condition was more likely to have been previously diagnosed during a screening exam.
- Clinical Features and Treatment Outcomes of Inflammatory CNV: Learn about the rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- Femtosecond LASIK for Correction of Low and High Myopic Astigmatism: Certain eyes had approximately four times more chances of undergoing retreatment due to dissatisfaction caused by residual refractive error.
- GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy: See what shorter foveal fluorescence lifetime features in eyes with loss of foveal sparing may correlate with.
- Industry News

A message from Review's Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was really scary until it wasn't. We had a small happy window of normalcy this spring when seemingly successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was crushed by the almost inconceivable reality of breakthrough infections that were not all mild.

And it seemed we were again adrift, not knowing how this would play out or how we'd get back the progress we'd made toward the goal of moving beyond COVID. At least the mortality rate remained relatively low if you were vaccinated.

We need to learn to live with COVID and to continue to enjoy life under different terms. But what are the terms? We're back to some of the same questions we had more than a year ago.

Can we go maskless outdoors? Can we crowd together in a theater or a concert or even a restaurant? If we get sick, how long should we isolate or should we isolate at all? For me, modifying how I live my life to reflect the new reality isn't the difficult part. It's not knowing what the right answer is. I can adapt, but not in the absence of data, of certainty. I'm holding onto my faith in science, in the many brilliant people working every day to help us get ahead of this pandemic. I trust them, and will willingly accept the next advance against COVID. Our only chance of survival will depend on science, and a shared effort to take care of each other. I'm worried, however, since we failed the latter effort in the past year. We'll see if we can belatedly learn that lesson—because we certainly need to.

Mark H. Blecher, MD
Chief Medical Editor
Review of Ophthalmology

Visit: JMI | Newsletter Signup
www.jhihealth.com/globalemail/
to sign up for Review of Ophthalmology Weekly News Update, and other e-newsletters distributed by Jobson Medical Information.

FOR ADVERTISING OPPORTUNITIES, PLEASE CONTACT

Michael Hoster: Mhoster@jobson.com
610-492-1028

Michele Barrett: Mbarrett@jobson.com
215-519-1414

Jon Dardine: Jdardine@jobson.com
610-492-1030
lifetime of fluorescence emitted by certain fluorophores within the eye, allowing for detection of subtle changes in metabolic as well as cellular activity.27

In FLIO, a short burst of light is used to excite certain molecules in the eye and then the system measures the time taken for the decay of the fluorescence from those molecules. AF lifetimes are excited at 473 nm and the device detects fluorescence decay in two separate wavelength channels. The long spectral channel (LSC), or red emission fluorescence (560 to 790 nm), records information from lipofuscin, while the short spectral channel (SSC)/green emission fluorescence (498 to 560 nm) records information from other fluorophores, including nicotinamide adenine dinucleotide (NAD), flavin adenine dinucleotide (FAD) and retinal carotenoids.27,28 Lens fluorescence impedes SSC, while LSC is relatively unaffected. It typically images an area of 30 degrees (256 x 256 pixels or 9 x 9 mm). A signal threshold of ~1,000 photons per pixel is essential for a good quality FLIO imaging, and it takes a total of two minutes per eye. FLIO lifetimes (FLT) are intensity independent, and FLT can be both prolonged or shortened in areas of low or high FAF intensity. An extensive literature review found that FLIO was particularly useful for four retinal conditions so far: AMD; Stargardt’s disease; hydroxychloroquine toxicity; and macular telangiectasia type 2.27

A ring-shaped pattern (1.5 to 3 mm from the fovea) of prolonged FLT is typically noted in an area called the MacTel2 zone (oval area 9 degrees vertical and 5 degrees horizontal, centered on the fovea).30 FLIO has shown to detect hydroxychloroquine toxicity at an early stage, prior to structural changes. A typical pattern of prolonged FLT, more pronounced on the SSC channel, can aid in early and easier detection of toxicity than multifocal ERGs. However, a complex fitting process and image analysis are a challenge at this stage for its use in clinical settings. This modality holds much promise in its application in a variety of retinal conditions in the future.

Quantitative Autofluorescence (qAF)

Conventional AF images record spatial distribution of the AF signal with designated pixel grayscale values between 0 and 255. A qualitative description of signal modulation has helped in the diagnosis and monitoring in various retinal disorders. However, with advances in technology, additional information could be acquired through a quantitative approach. The qAF approach measures the intensity of SW-AF along with spatial information, which allows for the distinction between disease-related changes from the normal age-related increase in retinal/RPE lipofuscin.12 By enabling comparison of AF intensities between individuals, and by using internal reference for long term follow-up, qAF helps address the shortcomings of conventional AF.31

Confocal SLO with a 30 x 30-degree field, 488 nm excitation and an emission range of 500 to 680 nm are used in a standardized approach for measuring qAF. A formula published by Dr. Delori’s group is used to cal-
culate qAF values. Selected images are aligned, averaged and saved in a non-normalized format. Different patterns can be used for the comparison of different retinal zones with different degrees of precision (Figure 3A). Trained and skilled operators as well as good quality images are essential for obtaining reliable qAF. Quantitative AF increases with increasing eccentricity 10 to 15 degrees from the fovea, with maximal values noted supero-temporally. qAF also differs among healthy individuals and is difficult to compare from one patient to another.12,31,33 It’s higher in females and whites; and lower in blacks and Asians likely due to increased melanin pigmentation in the RPE and the choroid. A non-linear rise in AF is observed between the ages 20 and 70. Repeatability in healthy eyes between two sessions was observed to differ by more than 6 to 11 percent on 5 percent of the occasions. Similar repeatability was observed in recessive Stargardt’s (10 percent) and Best vitelliform macular dystrophy (7 percent).14 Early and intermediate AMD patients had lower qAF values compared to healthy individuals.19 These qAF values in AMD patients were reliable and repeatable not just on the same day, but on follow-up visits at three and six months as well.

The widespread use of qAF is currently hindered because it requires a trained operator, installation of an internal fluorescent reference as well as appropriate software. Despite these limitations, qAF has enhanced the understanding of lipofuscin-related retinal disorders. A group led by Columbia University researcher Janet Sparrow, PhD,13 highlighted qAF’s utility in genotype-phenotype correlations as well as in guiding clinical diagnosis and genetic testing. It has the potential to serve as a biomarker for disease risk and progression (such as during chloroquine maculopathy,12 [Figure 3B]). They also believe that qAF can reflect visual cycle activity in various retinal diseases. If researchers and manufacturers can make this a technically less challenging process that’s easier to integrate into routine clinical practice, it may be able to enhance patient care to a great degree.

**Widefield Autofluorescence**

Widefield imaging is defined by a field of view greater than 50 degrees, and “ultra-widefield” is greater than 100 degrees.16 A field of view up to 267 degrees can be obtained thanks to montaging of different photographs. Clarus 500 (Zeiss) allows a field of view of 200 degrees by combining two 133-degree images, with blue and NIR-AF. Mirante (Nidek) has a field of view of 163 degrees and can perform multimodal imaging. Contact lenses can allow larger fields of view on a single image, but require the patient’s cooperation. The Heidelberg Spectralis imaging system uses the confocal scanning laser ophthalmoscope to obtain a 150-degree field of view with a contact lens attachment, allowing blue and NIR-AF. The Optomap ultra-widefield system (blue and NIR-AF) can obtain non-contact images of 82 percent of the retinal surface or up to a 200-degree field of view, but with spatial distortion. This system uses green AF (532 nm laser for excitation and 570 to 780 nm for the emission filter17 [Figures 3 and 4]), making it difficult to compare with other devices, and unable to distinguish between lipofuscin-like fluorophores (blue AF) or melanin-like fluorophores (blue-AF). It combines cSLO with an ellipsoid mirror to allow ultra-widefield imaging. The latter has two focal points, one close to the mirror and the second near the pupillary plane. Imaging through undilated pupils, short acquisition time (250 ms), and relatively better penetration through media opacity are additional advantages of the imaging system.38,39

With better imaging modalities, we’re now able to unearth many peripheral retinal manifestations of predominantly posterior pole diseases. For instance, peripheral AF abnormalities were noted in 63 to 69 percent of AMD cases. Central serous chorioretinopathy and Vogt Koyanagi Harada syndrome also had peripheral AF changes in 57 percent and 70 percent, respectively.18 Other uveitides40 (Figure 4B), choroidal tumors41 (Figure 4C), retinal detachment and retinoschisis42 have shown peripheral AF changes also. There are limitations to evaluating widefield AF, since peripheral abnormalities aren’t always disease-specific. For example, both healthy and AMD patients had peripheral AF abnormalities,43 and AF often can’t distinguish between peripheral RD or retinoschisis.44

However, widefield systems are beneficial for specific peripheral diseases such as inherited retinal diseases (Figure 4D). Standardized grading systems and genotype-phenotype correlations in different RP genotypes were formulated using ultra-widefield FAF systems.45–47 Similarly, atrophy expansion rates and age-dependent changes in the total lesion size were demonstrated using UWF-AF in patients with ABCA4 mutations.48–50

Future studies with this tool can highlight the clinical relevance of these peripheral changes and may thereby alter management guidelines.

In conclusion, fundus autofluorescence imaging has come a long way in recent years and continues to prove its worth as an invaluable tool for clinicians. Its expanding role in various retinal diseases, along with the emergence of newer imaging modalities such as FLIO and qAF, only serve to further highlight its potential. With continued advancements in technology and efforts to make these techniques more user-friendly, these modalities can have a wider use in clinical practice. Widefield AF has provided insights into the peripheral changes of diseases which were previously considered to have macular manifestations only. We believe that this imaging modality will continue to provide critical insights into the pathogenesis, diagnosis and management of retinal diseases, and should remain an essential adjunct tool in the armamentarium of clinicians.
visualize different retinal pigment epithelium alterations and imaging: A tool for biomedical research and diagnosis.


Dr. Borella is an ophthalmology resident and PhD candidate at the Department of Ophthalmology, University of Pittsburgh School of Medicine, and the Vison Institute, 15-20 National Ophthalmology Hospital and Sorbonne University in Paris, France. Dr. Vaidya practices at Dr. Vaidya Eye Hospital in Mumbai, India. Drs. Borella and Vaidya are co-first authors. Dr. Chhablani is a Professor of Ophthalmology at the University of Pittsburgh School of Medicine.
Since the development of anti-vascular endothelial growth factor injections, they’ve become the standard treatment for age-related macular degeneration, macular edema, diabetic retinopathy and retinal vein occlusion. Though physicians are adept at performing the injections, there’s always the risk for a possible complication. The use of intravitreal injection guides can potentially reduce subconjunctival hemorrhage while ensuring patient comfort.

“There are basically three functions that the guide should fulfill: First, to expose the injection site,” says, Harvey Uy, MD, medical director of Peregrine Eye and Laser Institute at the University of Philippines. “The second function is to identify the site of the injection, which is typically around 3.5 mm from the limbus. Thirdly is to allow you to inject at a set depth so that it limits the depth of the needle incursion.”

Here, we’ll take a look at some of the available injection guides.

**Precivia (FCI Ophthalmics)**
Precivia, originally called InVitria, is a single-use intravitreal injection guide from FCI Ophthalmics. This is a clear-plastic device placed on the patient’s eye without the need for a speculum, caliper or pressure plate. A guide tube with a fixed angle of 28 degrees and a fixed distance of 3.5 mm from the limbus allows ophthalmologists to safely inject without losing the position of the injection site. The cylindrical design has a rigid handgrip at the top for easier placement and stabilization, and the rounded base ensures that both eyelids are positioned properly for injection, the company says.

According to FCI, by gently pushing down and rotating the Precivia device, the eye becomes stabilized, which will create an anesthetic effect for the patient due to the pressure. Also, after the device has been positioned, the patient won’t be able to see when the needle is coming. After the needle is removed, by rotating the device again post-injection, the conjunctiva is replaced, and the injection hole is sealed.

In a prospective review of 200 intravitreal injections, 100 using Precivia and the other 100 using traditional methods, surgeons’ perceptions and patients’ intraoperative visual analogue scale (VAS) pain scores were recorded. The average VAS pain score in the Precivia group was 1.38 compared to 2.58 in the traditional group, which was statistically significant. Additionally, surgeons reported that insertion using Precivia was easy in 89 cases, moderate in 10 cases, and difficult in one case. The surgeons added that the device offered excellent globe stability and a safe, reproducible entry site and angle needle insertion.¹

**Rapid Access Vitreal Injection (RAVI) Guide (Katalyst Surgical)**
The Rapid Access Vitreal Injection Guide is a reusable, metal intravitreal injection guide. A baseplate at the end of the handle measures 7 mm by 7 mm. Two flanges on opposite sides of the baseplate hold the ocular structure, creating an injection site with a distance of approximately 3 to 4 mm from the limbus. After setting the device onto the ocular surface, the physician can safely make an injection through the 1.5-mm diameter aperture in the center of the baseplate.

The inventors of the RAVI Guide noted that the device can replace the function of both a lid speculum and caliper. In a prospective study to evaluate their device, the inventors along with a team of physicians performed 54 intravitreal injections using either the RAVI Guide or a lid speculum.

A faint line down the side of the Precivia device to the base of the guide tube can help physicians better position the device properly on the limbus.
They wanted to study patient acceptance of the device, complication rates and operative goals.

During the study, researchers had patients use the Wong-Baker FACES pain scale to rate their intraoperative treatments. The scale allows patients to choose from zero (no pain or discomfort) to 10 (severe levels of pain and discomfort), along with illustrated faces depicting emotions ranging from happy to sad. This simple rating scale helped researchers understand patient acceptance of the RAVI Guide compared to the speculum. In the RAVI Guide group, 72 percent (n=32) of patients had a pain-free experience compared to 64 percent (n=22) of patients in the speculum group. A pain score of two or higher was reported in 16 percent of RAVI Guide patients and 32 percent of speculum patients.

Researchers who designed the device conducted a retrospective review to compare the safety and efficacy of the guide. The study included 256 patients who underwent 992 intravitreal anti-VEGF injections over a two-year period. Of the total injections, 907 were done using the intravitreal guide, while 60 were done without it. A remaining 25 injections weren’t determined ahead of the study. Overall, local complications in the guide group consisted of one case of uveitis, one case of retinal tear and one case of amaurosis fugax. There were no local complications in the non-guide group. Researchers reported no major complications during the study. The researchers say that though all complications occurred in the Doi-Uematsu Guide group, the difference between groups wasn’t statistically significant.

**Doi-Uematsu Intravitreal Injection Guide (Duckworth & Kent)**

The Doi-Uematsu Intravitreal Injection Guide is a reusable guide suitable for right-handed surgeons, as the guide’s handle was designed to be held in the left hand leaving the right hand free for needle insertion. At the base of the handle is a 12-mm diameter ring with a “snow-tire” pattern for a firmer grip on the ocular surface and increased stabilization. According to D&K, there’s a 5.5-mm break in the ring that enables an anterior chamber tap, if required, in order to avoid intraocular pressure spikes. The guide hole is 0.5 mm in diameter, which is suitable for 27-gauge or smaller needles. This device is autoclavable.

Researchers noted that as the needle is withdrawn, the base plate may be slid over the conjunctiva to close the injection site if needed.

**Malosa Intravitreal Injection Guide (Beaver-Visitec International)**

The Malosa Intravitreal Injection Guide, designed by UAE surgeon Salman Waqar, is a single-use injection guide. According to Beaver-Visitec International, the guide is designed with a polycarbonate lash guard and a stainless-steel guide tube. The handle is shaped like a wishbone and positioned at a 45-degree angle to increase stabilization and ensure that it doesn’t become a disturbance during treatment.

“Aside from helping you inject anti-VEGF drugs, you can use it to guide you for injecting other medications such as antibiotics, for example, and it can also be used to help someone extract vitreous material from the posterior segment,” says Dr. Uy.

“Sometimes in an effort to further decrease patient discomfort, we might use a smaller needle,” continues Dr. Uy. “Typically, we use a 30-ga needle, but sometimes we can transfer the drug through a 31-ga needle. That’s smaller so it’s more comfortable, and sometimes before injecting triamcinolone—which is not a liquid but more of a suspension—we will use a larger-bore needle, like a 27-ga needle, so that we can inject the suspension more easily. And both the smaller and larger needles will go through the Malosa guide without difficulty.”

Dr. Uy and his colleagues conducted a clinical trial observing 200 adult
eyes undergoing intravitreal injection treatment. “We found two additional benefits when using the Malosa: One is that the patients report less pain compared to using the standard dual-blade eyelid retraction device,” says Dr. Uy. “Secondly, we saw less subconjunctival hemorrhage.”

During the study, 100 eyes were assigned injections using the Malosa Guide, and the other 100 eyes received treatment with a conventional dual-blade speculum and a surgical caliper. The study sought to compare the mean procedural time and complications when using either the guide or a speculum and caliper. The mean procedural time was shorter in the guide group (9.94 ±2.87 seconds) versus the speculum group (21.85 ±7.25 seconds). Dr. Uy reported that the rate of post-injection subconjunctival hemorrhage was higher in the speculum group, for which he had no explanation. No other injection-related adverse reactions were observed in either of the patient groups. 4

“Physicians’ workloads are very heavy, especially with regard to the need to inject a lot of patients,” says Dr. Uy. “However, injections shouldn’t hinder physicians’ work of seeing patients and doing other procedures in the clinic. So, if we can find a way to minimize the time to do the injections, that’ll make our workflow more efficient.”


DISCLOSURES

Dr. Uy has no financial interests to disclose.
A young woman presents with sudden-onset blurred vision and metamorphopsia in one eye.

MARA E. PENNE, MD, AND CAROL L. SHIELDS, MD
PHILADELPHIA

Presentation
A 29-year-old Caucasian female with sudden onset of blurred vision and metamorphopsia in her left eye presented for ophthalmic evaluation. She was 20 weeks pregnant at presentation. She denied any history of trauma. She denied any concurrent pain, headache, diplopia, flashes, floaters or photophobia. She denied any symptoms in the right eye. Systemic review of symptoms was negative. Of note, her pregnancy had been uncomplicated up to this point.

History
Past ocular history included myopia in both eyes. Past medical history disclosed celiac disease. Family history included a mother with melanoma of the skin, maternal grandmother with colon cancer, and maternal grandfather with bladder cancer. Social history was significant for rare alcohol consumption, but was otherwise unremarkable. She did not have any known drug allergies. Current medications included pre-natal vitamins.

Examination
The patient’s vital signs were within normal limits. Ocular examination demonstrated best-corrected visual acuity of 20/20 in the right eye and 20/25 in the left eye. Pupils were equally round and reactive in both eyes without afferent pupillary defect in either eye. Intraocular pressures were 10 mmHg in both eyes. Confrontation visual fields were full in both eyes. Extraocular motility was full bilaterally. The anterior segment examination was largely unremarkable and didn’t reveal any abnormalities.

Dilated fundus examination of the right eye demonstrated a normal optic disc, macula, vessels and peripheral retina (Figure 1). The left eye demonstrated a normal optic disc, macular edema with hard exudation, as well as venous dilation and tortuosity inferiorly. Peripheral examination in the left eye revealed a 4x4 mm retinal vascular mass at 5:00 with dilated feeding and draining vessels, as well as additional exudation extending into the periphery (Figure 1).

What’s your diagnosis? What work-up would you pursue? The diagnosis appears on the opposite page.
Ancillary imaging was obtained including optical coherence tomography (Figure 2) and ophthalmic ultrasonography of the left eye (Figure 3). OCT of the left eye demonstrated macular edema in the outer nuclear layer with associated hard exudation in the outer plexiform layer and shallow subretinal fluid involving the fovea. Ultrasonography revealed an echodense retinal mass with 3.7 mm basal diameter and 1.7 mm retinal thickness.

The differential diagnosis in this patient with unilateral vision loss, found to have a retinal vascular lesion associated with macular edema and hard exudation, includes retinal hemangioblastoma (RH), cavernous hemangioma, acquired vasoproliferative tumor, choroidal hemangioma and retinal racemose hemangiomatosis. Given the dilated and tortuous feeder vessels of the lesion, the presence of associated exudation, and the lack of other ocular conditions, a diagnosis of retinal hemangioblastoma was made. Treatment options, including verteporfin-enhanced photodynamic therapy, fluorescein-enhanced argon laser photocoagulation, transpupillary thermotherapy, cryotherapy and radiotherapy were discussed. The patient chose to defer treatment until the post-partum period. Genetic testing for von Hippel-Lindau (VHL) syndrome was performed and was negative.

At the seven-month follow-up visit, now three months post-partum without any intervention, the patient reported a subjective improvement in her vision. Visual acuity OS improved to 20/20 from 20/25 on initial presentation.
fundus examination revealed a vascular lesion, stable in size, with persistently dilated vessels. OCT demonstrated spontaneous resolution of the macular edema and exudation. The patient continued to defer treatment until cessation of breastfeeding one year from presentation (seven months post-partum). At this time, visual acuity was 20/20 and OCT showed a flat macula without exudation. The RH tumor was unchanged in size. Transpupillary PDT was performed. On postoperative day #1 the patient presented with a visual acuity of 20/400 OS and was found to have severe cystoid macular edema with an exudative retinal detachment (Figure 4). She was treated twice with intravitreal ranibizumab with resulting resolution of the macular edema and retinal detachment. At the most recent follow-up visit, seven years from initial presentation, visual acuity in the left eye was 20/30. Examination and imaging demonstrated a regressed fibrotic retinal lesion measuring 3 mm × 3 mm with nontreated feeder vessels and without the presence of macular edema or exudation (Figure 5).

Discussion
Retinal hemangioblastoma is a benign, slow-growing retinal vascular tumor that appears clinically as a red–orange mass. This tumor classically presents with prominent feeder vessels extending from the optic disc and can be located in the peripapillary or peripheral retina. This tumor can be associated with accumulation of subretinal fluid, sub- and intraretinal exudation, and vitreoretinal fibrosis, which can result in profound visual loss. The exudation often accumulates in the macula and presents as a macular star. Diagnosis can typically be made on dilated fundoscopic examination, though additional imaging is helpful, particularly in the cases of small tumors. In some cases, this tumor can be detected on fluorescein angiography as hyperfluorescent, before it becomes symptomatic. Biopsy isn’t required for diagnosis.

Clinical onset occurs most commonly in the first three decades of life. Importantly, retinal hemangioblastoma can be associated with VHL syndrome, and a thorough workup is required for any case of suspected hemangioblastoma. VHL syndrome is an autosomal dominant disorder caused by a mutation in the VHL tumor suppressor gene, located on chromosome 3. This mutation has a prevalence of 1 in 40,000 to 50,000. Detection of these tumors by an ophthalmologist is critical, as 70 percent of individuals with VHL syndrome are diagnosed by detection of RH tumors. This prompts a full systemic workup for other tumors, including renal cell carcinoma, which constitutes the greatest cause of mortality in these patients.

Treatment for RH is varied and depends on the size and location of the tumor, as well as the VHL association. Some believe that this tumor can be safely observed in select cases when asymptomatic without subretinal fluid. However, most are treated and those with VHL association tend to be more aggressive. Those near the macula can lead to profound vision loss, and thus also require prompt treatment. Treatment methods vary based on tumor size. Small lesions (<3 mm) can be treated with laser photocoagulation or PDT; medium lesions (3 to 6 mm) can be treated with PDT or cryotherapy; and large (>6 mm) lesions can be treated with PDT, plaque radiotherapy or internal resection by pars plana vitrectomy. Therapy with PDT can be associated with a transient exudative response, as was noted in 24 percent of patients in a recent case series of 17 patients. Anti-vascular endothelial growth factor (VEGF) therapy is useful in treating macular edema and subretinal fluid, but has no demonstrated effect in reducing tumor size.

This case was unique in that our patient initially presented with an RH tumor during pregnancy; similar cases are not well-documented in the literature. She demonstrated a spontaneous resolution of secondary macular edema post-partum, as has been seen in cases of macular edema associated with other underlying conditions such as diabetic retinopathy and circumscribed choroidal hemangioma. The tumor remained stable in size; however, treatment was deemed necessary due to the threat of recurrence of subretinal fluid.

In conclusion, retinal hemangioblastoma can present with decreased visual acuity, commonly secondary to macular edema with exudation, as was the case with our patient. For those tumors diagnosed in pregnancy, spontaneous resolution of subretinal fluid may occur in the postpartum period. Treatment modalities vary based on size, location and association with VHL syndrome. Management with PDT, which is used to treat tumors of all sizes, can cause a transient exudative response. Anti-VEGF therapy can be useful in treating associated macular edema and subretinal fluid. 

As eye care professionals, eye drops play a central role in the care we provide for our patients. Many prescription and OTC eye drops continue to include preservatives—compounds that are proven deleterious to the ocular surface.

Preservative Freedom is a commitment to preserve patient eye health.

We’re pledging to break through our indifference and old habits, and to do so while keeping our patients’ eye care as the highest priority.

ALL THOSE IN FAVOR OF PRESERVATIVE FREEDOM, SAY EYE

Learn more, and join the movement at PreservativeFreedom.com
Prepare now at iyuzeh.com