

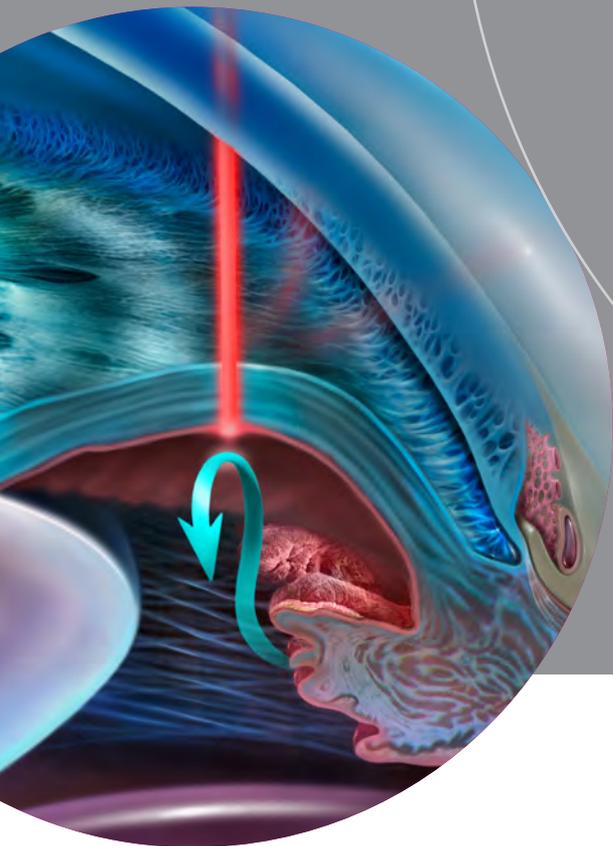


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DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa[®] and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa[®] dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa[®]-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

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

References: 1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. 2. MMIT:12/2018.



RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS

Bacterial Keratitis

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

Use with Contact Lenses

RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

Clinical Trials Experience

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata

Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥ 0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥ 3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation

There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.



Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.
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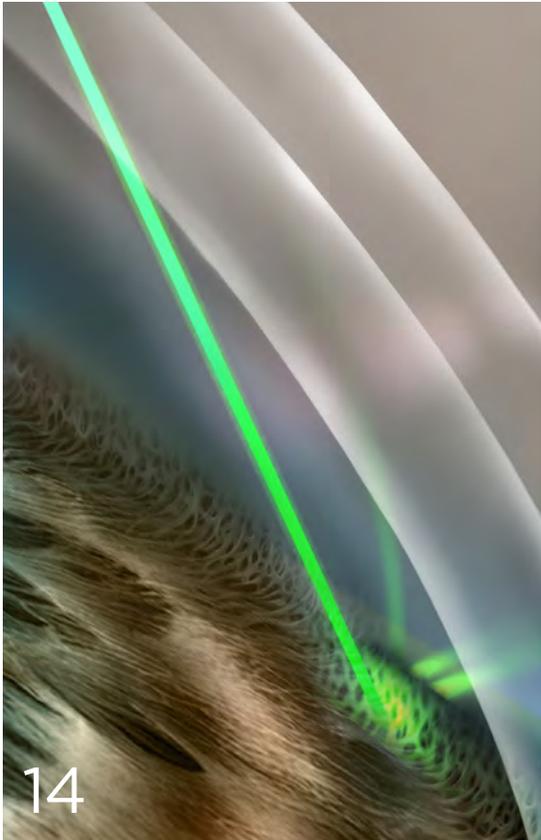
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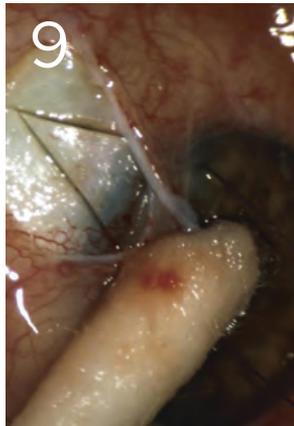
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Originally published in July and August 2020.

COVER ILLUSTRATION

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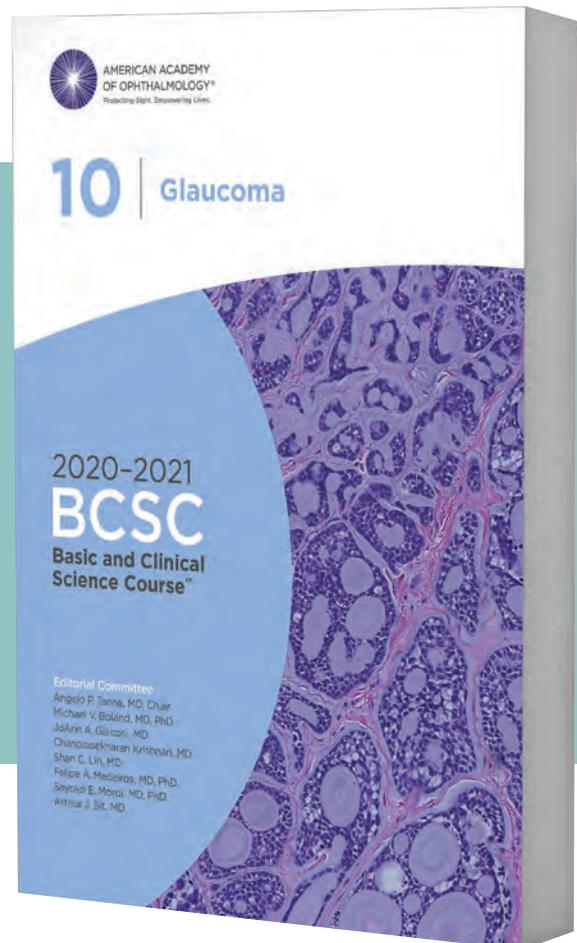
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Perimetry Goes High-Tech and Mobile

Perimetry is a critical part of managing glaucoma, but traditional testing can present a challenge, especially for any patient who is unable to hold still long enough—or press the right buttons—for an accurate test. Moreover, the equipment used for standard automated perimetry (SAP) testing is costly and bulky.

Enter several novel platforms based on smartphone and virtual reality (VR) technology. As these high-tech, mobile systems are still in development, their eventual role has yet to be defined. For instance, will they replace SAP, or serve as an adjunct? Will they be used primarily in resource-poor areas? And what about individual home-based monitoring—or, at the other extreme, glaucoma screening in large populations?

Tracking Eye Movements

Eyecatcher, a tablet-based visual field (VF) test with a built-in eye-tracking camera, assesses how well a patient's reflexes respond to flashing lights onscreen.¹

“When it comes to speeding up the way we can offer new therapies to patients, what we need is a very efficient way of measuring change in patients on a certain therapy,” said David P. Crabb, PhD, MSc, head of the Crabb Lab at City, University of London (CUL),

where Eyecatcher was developed. “One of the main aims of the Eyecatcher is to simplify how this measurement is done and make it more accessible.”

When using the Eyecatcher, patients don't need to press buttons; they simply follow a spot of light on the tablet. The person's eye movements are then used to assess the VF. “It's not a replacement for current testing technology, but it

does have potential as a case-finding or triage-type device to better direct resources toward people suspected to be at risk for loss of vision,” Dr. Crabb said. The Eyecatcher also might allow clinicians to focus their energy and skills on treatment instead of screening. “One of our goals is to create a perimetry assessment that doesn't require glaucoma specialists,” Dr. Crabb said.

Cost. “The traditional instruments that clinicians use cost \$15,000 to \$30,000, and we're offering a lower cost, more patient-friendly alternative,” Dr. Crabb said. “Eyecatcher is a \$400 tablet computer with a \$100 eye-tracker camera.”

Given the Eyecatcher's other advantages—small size, portability, and ease of use—it may well prove to be useful in low-resource communities. And Dr. Crabb believes that the Eyecatcher



FAST AND RELIABLE. The smartphone-based PeekCS test offers an easy, rapid, and reliable way to test contrast sensitivity.

could be especially helpful in areas in which patients must pay for part of their care. “A challenging test is even more of a concern when patients have to pay [out of pocket] to perform a test they find very difficult to do,” he said.

Next step: Home monitoring? CUL researchers also are researching the validity of home testing to gather accurate data, with patients taking Eyecatcher tablets home to test their own vision more frequently. “We've deliberately not supported them too much, other than giving them basic instructions, so next year we'll find out if they're actually using it or not,” Dr. Crabb said.

“Home monitoring for people with glaucoma hasn't yet been studied with real scientific validity, such as discovering what patients actually do when you send them home with a new high-tech device,” he noted. In a previous home monitoring study that used a web-based diary tool, a number of patients reported feeling anxious about their glaucoma, and one wanted to leave the study

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BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING NIGEL M. BOLSTER, PHD, DAVID P. CRABB, PHD, MSc, AND RICHARD K. LEE, MD, PHD.

because it led to obsessive rumination about visual loss.²

“Glaucoma clinics are already very busy, which will get worse as the population ages,” Dr. Crabb said. “Home monitoring is likely to be better than eye exams once or twice a year, but we need to get the assessments and technology right. More research is needed to see if the benefits outweigh the monetary and clinical costs.”

He added, “A lot of the tests we use in the clinic would benefit from being upgraded into technology we now have in our homes, such as smartphones and tablet computers.”

Putting VR to Work

Another approach to VF testing involves a VR headset and a smartphone. This system uses frequency doubling technology (FDT), which is thought to stimulate the retinal ganglion cells most sensitive to glaucomatous damage.³ A head-mounted VR display, a high-resolution smartphone, and a Bluetooth-enabled remote combine to run a mobile application based on the FDT C-20 screening protocol.³

“This screening device is part of the Portable Ophthalmologist Project (POP) at the Lee Lab to create portable, environment-hardened, low-cost technologies for vision screening and diagnosis that are critical for international and community ophthalmology in low-resource, remote, or large populations,” said Richard K. Lee, MD, PhD, head of the Lee Lab at the Bascom Palmer Eye Institute in Miami. “The goal is ultimately an ophthalmologist’s office in a backpack.”

The device produces frequency doubling stimuli at 30 Hz with contrasts similar to the Humphrey Zeiss FDT.³ In one study, testing on 19 eyes showed no significant difference in detecting glaucoma compared to the Humphrey Zeiss FDT; the authors suggested that primary open-angle glaucoma patients could be identified using a smartphone-based VR headset.³

Cost. This mobile virtual perimetry FDT device cost less than \$130 to build. Patient data are stored locally on the smartphone or transferred to the cloud for integration into an electronic health

record. An additional benefit: It can be used in areas without reliable electricity.

“This low-cost, portable technology is self-contained within a VR goggle and can upload data to the cloud in a HIPAA-compliant manner for longitudinal care in any type of environment around the world,” Dr. Lee said. “It can also be used for handicapped patients who cannot sit in a regular station for formal VF testing, for ICU patients in bed, and for other patients with physical limitations or medical issues.”

Testing Contrast Sensitivity

Another high-tech, mobile option for glaucoma screening: a smartphone-based contrast sensitivity (CS) test called the PeekCS.

“It’s based on the PRCS (Pelli-Robson Contrast Sensitivity test), the gold standard for testing contrast sensitivity,” said Nigel M. Bolster, PhD, with Peek Vision in London, developer of the PeekCS. “Currently, all of our global blindness metrics are based on measurement of distance visual acuity (VA), but that only tells part of the picture of a patient’s vision.” And although CS testing can help measure visual defects in glaucoma patients, it is infrequently measured in routine clinical practice.⁴

The PeekCS uses the Android OS with a “tumbling E” format. With a smartphone mounted on a tripod, the tester swipes the screen in the direction the participant pointed—a useful methodology for cross-cultural or low-literacy patients. The test was recently validated in a study of 147 patients with a mean age of 50.3 years (range, 18-82 years) who had been affected by trachoma.⁴ The PeekCS measurements were highly correlated with those obtained with the PRCS test.

Why focus on contrast sensitivity?

Dr. Bolster offered one scenario: “After cataract surgery, some patients receive a tiny increase in VA [postoperatively] and can’t thank that doctor enough, whereas others come in and get a big increase in VA but aren’t nearly as happy,” he said. “We hypothesize that a lot of this is due to a lack of perceiving contrast.”

An increase in the number of aging adults is expected to increase the number of cases of impaired CS due to glaucoma, macular degeneration, and diabetic retinopathy, even when patients have normal VA.⁴ “We think CS testing, when combined with other low-cost tests, could be useful for detecting potential glaucoma cases and other degenerative eye diseases, and of great advantage in determining a more accurate view of quality of life based on a patient’s vision,” he said.

The overall goal? “We’re seeking to address the looming global eye health crisis, with 2.2 billion people who have vision impairment or blindness worldwide,” he said.

Additional VA test. The team has also developed a VA test called Peek Acuity. “We’ve been able to quickly train nonclinical staff to conduct the test with a high degree of accuracy and repeatability,” Dr. Bolster said.

He added, “Peek Acuity has been classified as a Class 1 medical device and is available as a free download from the Google Play Store. It’s part of a broader suite of technology-enabled tools and processes designed for eye care providers in remote and low-resource settings.”

1 Jones PR et al. *Trans Vis Sci Tech.* 2019;8(1):17.

2 McDonald L et al. *J Ophthalmol.* 2017;2017:8452840.

3 Alawa KA et al. *Br J Ophthalmol.* Published online Sept. 17, 2019.

4 Habtamu E et al. *Trans Vis Sci Tech.* 2019;8(5):13.

Dr. Crabb is head of the Crabb Lab in the Division of Optometry and Visual Science at City, University of London in the United Kingdom. *Relevant financial disclosures: Fight for Sight: S.* Dr. Bolster is head of product design and research at Peek Vision in London. *Relevant financial disclosures: Peek Vision: E.* Dr. Lee is Walter G. Ross Distinguished Chair in Ophthalmic Research and associate professor of ophthalmology at the Bascom Palmer Eye Institute in Miami. He also holds secondary appointments in the Department of Cell Biology and Anatomy and in the Neuroscience Program at the University of Miami. *Relevant financial disclosures: None.*

See the disclosure key, page 5. For full disclosures, see this article at aao.org/eyenet.

MD Roundtable: The Enduring Role of Traditional Glaucoma Surgery, Part 1

With the advent of minimally invasive glaucoma surgery (MIGS), glaucoma treatment paradigms are changing. However, the traditional surgical procedures—trabeculectomies and tube shunts—still have an important place in glaucoma management. In this two-part article, Ruth D. Williams, MD, of the Wheaton Eye Clinic, hosts a discussion with Anne L. Coleman, MD, PhD, of University of California, Los Angeles (UCLA), and Dale K. Heuer, MD, past president of the American Glaucoma Society. This month, they share their perspectives on the current status of trabeculectomy surgery, when to opt for it, how to talk with patients about risk, and the importance of postoperative management. Part 2 will appear in the next issue.

Decreasing Number of Trabeculectomies

Dr. Williams: *The Medicare database shows that the number of trabeculectomies being performed in the United States is declining. Does that reflect your clinical experience?*

Dr. Heuer: Yes. I have had numerous patients over the last five to seven years in whom I historically would have done a trabeculectomy that I would now instead refer to one of my colleagues for a less invasive procedure. So, in my

practice (from which I should note that I recently retired), I did see a trend toward fewer trabeculectomies, at least in patients with mild to moderate glaucoma.

Dr. Coleman: We've seen that at UCLA, too. I think that there is a role for MIGS in individuals who have earlier-stage glaucoma. In the past, we might have done a trabeculectomy in some of these patients, but now we're doing a different procedure.

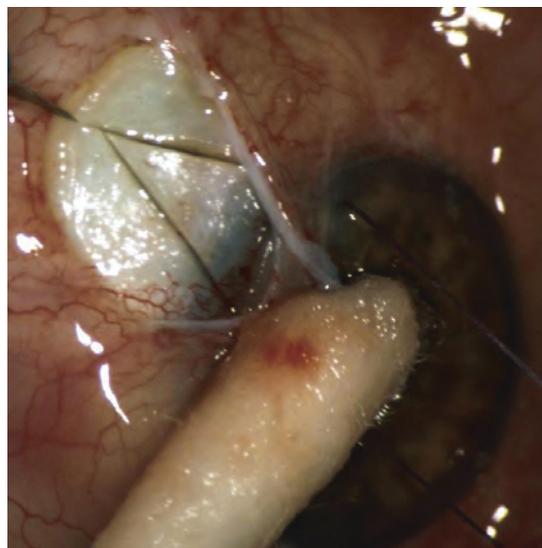
When to Choose Trabs

Dr. Williams: *What are some clinical situations in which you think a trabeculectomy is still the best procedure?*

Dr. Coleman: I am still doing trabeculectomies in patients with very advanced glaucoma because I want a very low intraocular pressure. In my hands, I still get a lower eye pressure by performing a trabeculectomy with mitomycin C than with any other procedure.

Dr. Williams: I agree, the best way to get a very low pressure is with trabeculectomy, and with our trend of setting lower target pressures, its role becomes more precise.

Dr. Heuer: I concur, and I think that what we lack is a randomized study



TRABECULECTOMY. *The number of trabeculectomies performed each year is on the decline, but it's still important to learn this technique and keep skills sharp.*

comparing trabeculectomy with MIGS procedures. In the absence of that, the best data we have come from a study by Schlenker and coworkers published a few years ago.¹ They found that white patients, those with poorer preoperative vision, and those with more advanced glaucoma had better outcomes with trabeculectomy than with the gel stent. Actually, that last factor was only of borderline significance, so we may want to consider the gel stent in our patients with better vision, even those with more advanced glaucoma.

Talking to Patients About the Risks

Dr. Williams: *We know that our patients read about the glaucoma*

Originally published in July 2020

ROUNDTABLE HOSTED BY RUTH D. WILLIAMS, MD, WITH ANNE L. COLEMAN, MD, PHD, AND DALE K. HEUER, MD.

treatment options on the internet. In fact, patients sometimes come in telling us which MIGS procedure they want. They are also reading that MIGS procedures have a lower complication rate than trabeculectomy. How does this affect your conversation with the patient regarding the risks of traditional surgery?

Dr. Heuer: I think that the conversation about possible complications with any glaucoma procedure is always a little more protracted than, for example, with cataract surgery, where we have a more predictable outcome. We always have to put the risks and benefits in the context of what the alternative is, and if the alternative is going blind—albeit more gradually from their glaucoma—it makes the decision a little easier. I do

“One thing I do is make sure that patients who undergo trabeculectomy understand the lifelong need for good hygiene.”

think that by preparing patients for the worst, lowering their expectations, we often have a smoother outcome post-operatively—most of the patients end up thinking, “Well, that wasn’t nearly as bad as the doctor said it would be.”

Even with patients for whom we think that trabeculectomy is a better option than the less invasive approaches, it’s still always about risk and benefit. But if the patient feels strongly otherwise or is very risk averse, I may say that, as long as we’re not going to burn any bridges, we can try something else—and do a trabeculectomy later, if needed.

Moreover, another issue is that many of the MIGS approaches are indicated only in combination with cataract surgery, and many of our patients are already pseudophakic or may not even have a cataract.

Dr. Coleman: Another big issue is that with trabeculectomies, it’s important to make sure that the patient understands the long-term risk of endophthalmitis. I think that doesn’t always show up in randomized controlled clinical trials because of the short follow-up. The studies are not usually designed to be long enough to see cases of endophthalmitis that may develop in a patient 10 or more years

post-op. One thing I do is make sure that patients who undergo trabeculectomy understand the lifelong need for good hygiene.

Trabs: The Importance of Post-op Management

Dr. Williams: One of the most important skills for successful trabeculectomy outcomes is postoperative management, unlike MIGS, where in most cases, you don’t have a lot to manage afterward. The three of us have done so many trabeculectomies that we’re probably not rattled when we have a shallow chamber or a bleb leak; we have the experience to know how to manage it.

Both of you have been training residents and fellows for a long time.

Do you think our glaucoma fellows and residents have seen enough post-op management of trabeculectomies to be comfortable with the procedure going forward?

Dr. Coleman: That probably depends on the training program. At UCLA, our residents still do trabeculectomies. The fellows at UCLA also do a lot of trabeculectomies because our glaucoma faculty still do mainly trabeculectomies and shunts, although fewer than in the past because of the increase in MIGS cases. I think that one of the reasons why individuals choose to do a glaucoma fellowship at UCLA is that they’re aware that we still do a lot of trabeculectomies and shunts.

Dr. Heuer: I think the experience is quite variable. It’s important for anyone going into a comprehensive ophthalmology practice—particularly if they’re not located in a major urban area—to develop a level of comfort with trabeculectomy to be able to manage the complications. Even if a comprehensive ophthalmologist sends her patients some distance to a specialist for the procedure, she might need to be involved in some of the postoperative care and will probably be responsible for the long-term follow-up.

I’d like to think that our training programs are adequately preparing all

residents and fellows, but those who are not connected with a county hospital or busy VA hospital may not be getting enough exposure to trabeculectomy.²

Ironically, I think that the fellows, who are training with some of our higher-profile colleagues who do a lot of the less invasive approaches, may be in a kind of a bubble, in which they’re not being exposed to as many trabeculectomies or shunts. This is a loss because they will probably need these skills in two or three years, when some of the patients who underwent MIGS procedures will need to undergo traditional filtering surgery.

Dr. Williams: This is my advice to people in training who have the opportunity to learn trabeculectomy: During this time of excitement about learning the latest MIGS procedure, be just as excited about learning how to do a good trabeculectomy. I think that all three of us would agree that filters are here to stay.

Dr. Coleman: I agree. And I think it’s important to be prepared for the most complicated patients when you’re a glaucoma specialist. Even though trabeculectomy may not be as popular 10 years from now, it might still be the only thing we have for some cases.

1 Schlenker MB et al. *Ophthalmology*. 2017;124(11):1579-1588.

2 AUPO Fellowship Compliance Committee. Exit Survey Reports: Glaucoma 2014-2019. <https://aupofcc.org/fellowship-programs-residents-subspecialties/glaucoma>; click “Fellow Surgical Volume Report,” then “Procedures reported by Glaucoma Fellows in Exit Surveys 2014-2019.”



Dr. Coleman is president of the American Academy of Ophthalmology and a glaucoma specialist at UCLA, Stein Eye Institute.

Financial disclosures: None.



Dr. Heuer is past president of the American Glaucoma Society. Financial disclosures: National Eye Institute: S; Santen: S.



Dr. Williams is a glaucoma specialist at Wheaton Eye Clinic, Wheaton, Ill., and the Chief Medical Editor of *EyeNet Magazine*.

Financial disclosures: None.

See the disclosure key, page 5.

MD Roundtable: The Enduring Role of Traditional Glaucoma Surgery, Part 2

In the second installment of this two-part article about traditional glaucoma surgery, Ruth D. Williams, MD, of the Wheaton Eye Clinic, continues the conversation with Anne L. Coleman, MD, PhD, of University of California, Los Angeles (UCLA), and Dale K. Heuer, MD, past president of the American Glaucoma Society. They talk about complications to watch for in trabeculectomy (and MIGS), tubes, how important it can be to learn techniques from colleagues, and future directions for filtering surgery.

Long-Term Complications

Dr. Williams: One of the advantages of trabeculectomy is that it's not very expensive. From a population health perspective, compared to many of our MIGS options, filters are more cost-effective. Dr. Coleman, as an expert in public health, how does this factor into your decision-making?

Dr. Coleman: Yes, it is less expensive right now. However, I don't know if I would go out and do trabeculectomies in certain environments; the opportunity for consistent, good hygiene needs to be available as does access to eye care. This is something to be aware of: The way specialists are able to practice at state-of-the-art centers may be very different from how a general oph-

thalmologist practices in a remote area.

I really do worry about the long-term risk of endophthalmitis, so I think that it will be beneficial if we develop newer procedures that are less invasive than trabeculectomies or even some of today's MIGS that create blebs.

Dr. Heuer: I'd like to follow up on that last thought about MIGS. One of my mentors, Paul Palmberg, talked about "the curse of long-term follow-up," and we're already starting to see some longer-term problems with MIGS. For example, there are a couple of case reports of gel microstent devices that have eroded through the conjunctiva, and with that comes the risk of endophthalmitis. So, it's like everything in glaucoma: There's an initial enthusiasm and then reality starts to set in. Over time we'll have a better sense of where these procedures fit.

All of our patients who are undergoing any procedure that has a subconjunctival filtration approach need to be aware of the symptoms of bleb infection. One of my other mentors, Richard Parrish, taught me the mnemonic "RSVP," for Redness, Sensitivity to light, Vision change, and Pain. I added another P for Pus, so it's RSVP



TUBE SURGERY. In contrast with trabeculectomy, aqueous shunt surgery is slightly on the rise.

squared. Patients really get that, and I put it in the visit summary notes for everyone who's had a trabeculectomy.

Dr. Coleman: And we need to keep reminding our patients. We may have told them at one point; however, they may forget. So repeating that message is very important.

Tubes Versus Trabs

Dr. Williams: If we look at the Medicare database, the number of tubes being done is increasing slightly over time. Why are the number of trabeculectomies decreasing, but the number of tubes has been stable or increasing over time?

Dr. Heuer: I think, in part, that MIGS has displaced more patients who might have been classic trabeculectomy candidates than classic aqueous shunt patients. Also, because of the outcomes

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ROUNDTABLE HOSTED BY RUTH D. WILLIAMS, MD, WITH ANNE L. COLEMAN, MD, PHD, AND DALE K. HEUER, MD.

of the Tube Versus Trabeculectomy (TVT) study and the Primary Tube Versus Trabeculectomy (PTVT) study, we may be a little more inclined to do a tube in some patients in whom we otherwise might have done a trabeculectomy.

Dr. Williams: Let's talk more about how the TVT and PTVT studies affected your choice of procedures.

Dr. Heuer: I should disclose that I am a cochair of both of those studies. But even with the findings, I think there's still a bias toward trabeculectomy. Although the five-year results from TVT and three-year data from the PTVT suggest that tubes do much better than we historically thought (based on the fact that we were initially using them in very high-risk situations), I have to admit that I would probably still have a trabeculectomy. Glaucoma is a very long-term issue, and if the trabeculectomy fails, moving on to a tube is a logical sequence. However, if I have an aqueous shunt first and that doesn't work, in most patients it will probably be technically more difficult to perform trabeculectomy. We've learned a lot of things, even since the TVT/PTVT studies were designed, that make trabeculectomy a little safer than it was in those studies.

Dr. Coleman: I think that's true. At a meeting I saw a video by one of the surgeons in the TVT study, and the trabeculectomy was done very differently from the way some of the faculty do it at UCLA. The different ways that people are trained to do their trabeculectomies could have influenced the results in that study because the trabeculectomies weren't really standardized.

Dr. Heuer: Well, I'm not sure you can standardize it completely, but having said that, you're right.

Dr. Coleman: But you could standardize the size of the scleral flap. You could potentially standardize the size of the sclerostomy and the conjunctival closure.

Dr. Williams: Although you could standardize techniques for a study, one of the things that makes great surgeons is that we figure out what works in our hands—and what you figured out might be different from what I figured

out. You really want a surgeon to do what works best for him or her. And we're such individualists, and very particular about our techniques, that even if you standardize a procedure, the best outcome might be achieved when the surgeon has developed as his or her own expertise.

Dr. Heuer: This reminds me of a phrase that I think was coined by Doug Rhee: "artisanal surgery." And if it was ever true of anything, it's trabeculectomy!

Dr. Coleman: I agree. I think one reason that procedures like drainage devices and MIGS are so popular is because they are more standardized procedures that can be done by an eye surgeon. It is harder to standardize an "artisanal" technique like trabeculectomy.

Dr. Heuer: Trabeculectomy techniques have also evolved. If you look back to when we started the TVT study, many people were still doing a lot of limbus-based flaps. There are occasions where I still prefer a limbus-based flap—for example, if someone has a gossamer-thin conjunctiva—but I think most of us have switched to fornix-based flaps with some modifications. Perhaps even the way the mitomycin was applied in the study may not reflect the current approach; many of us have migrated to using injection rather than sponges. Furthermore, the concentration of mitomycin tends to be individualized based on our assessment of each patient's scarring risk-profile, such that lower concentrations are used in many patients than the 0.4 mg/mL concentration that was applied with sponges in the TVT study.

Learning From Colleagues

Dr. Williams: *One of the great advantages of having colleagues and watching them do surgery or seeing their post-ops is that we bring training from different programs and learn how to do things differently. I've found it very enriching to learn different techniques and the varied approaches from the glaucoma specialists in my practice.*

Dr. Heuer: Something has been lost since the dark ages when I came out of

training. At that time, an ophthalmologist going into practice would often serve as an assistant, whether it was for cataract surgery or another procedure, so there was cross-fertilization. Now that we're in the era of ambulatory surgery centers and no assistants, we've lost some of that. So, as Dr. Williams suggests, you should avail yourself of that opportunity whenever you can.

Dr. Coleman: In my experience, my colleague Joseph Caprioli and I trained at different places. When he came to UCLA about 20 years ago, we were very different in terms of how we operated, but over the years, and with the cross-fertilization of the fellows, we now operate more similarly, according to the fellows.

Looking to the Future

Dr. Williams: *In closing, can you imagine a time when either trabs or tubes are no longer performed or no longer necessary?*

Dr. Coleman: I can, because I think people are going to work on a cure. I think that's really what the public expects, what patients want, and really what I want.

Dr. Heuer: We've been putting a hole in the eye wall for over 150 years, and so I hope that time does come. Still, I think there will be niche diagnostic categories where something akin to trabeculectomy or perhaps aqueous shunts will be necessary. But maybe a hundred years from now, doctors will look back and say, "My goodness, how in the world could they bring themselves to do that to the eyes?"

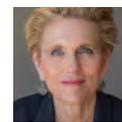


Dr. Coleman is president of the American Academy of Ophthalmology and a glaucoma specialist at UCLA, Stein Eye Institute.

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Dr. Williams is a glaucoma specialist at Wheaton Eye Clinic, Wheaton, Ill., and the Chief Medical Editor of *EyeNet Magazine*.

Financial disclosures: None.

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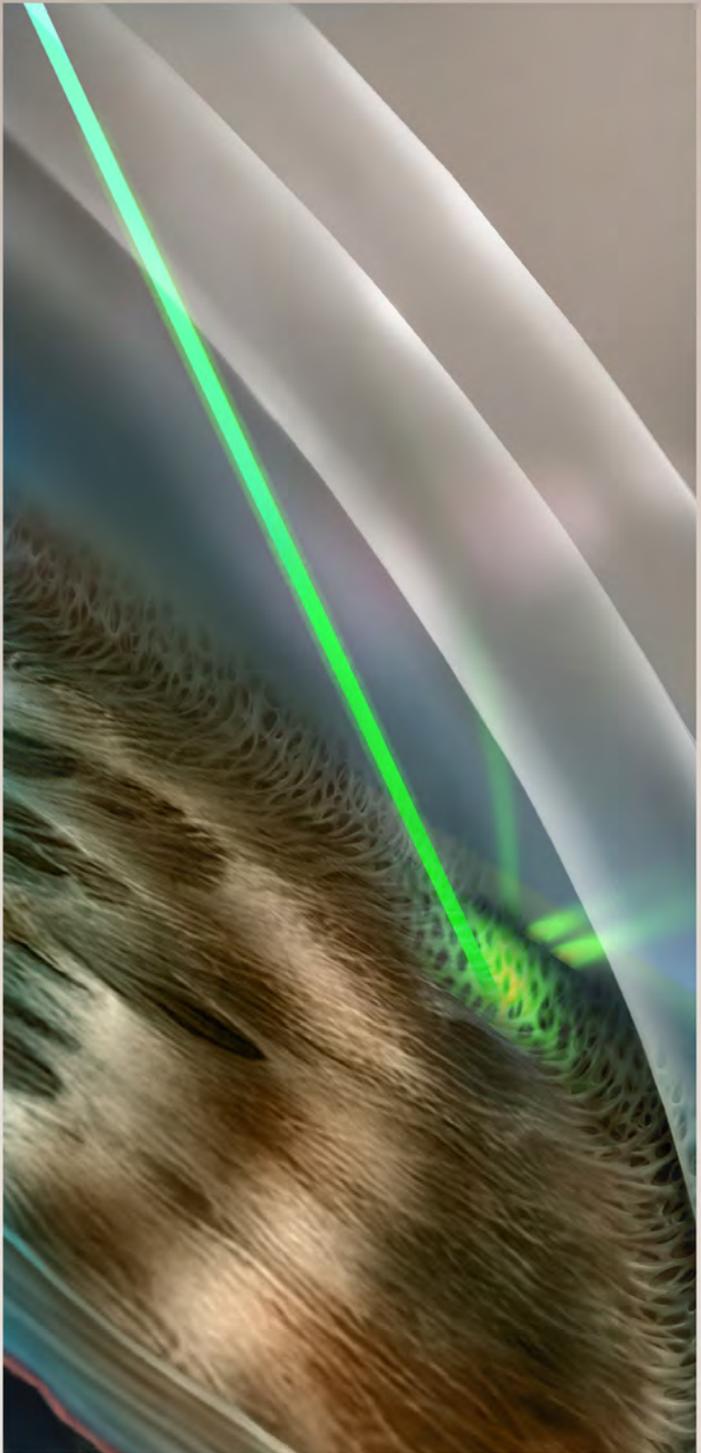
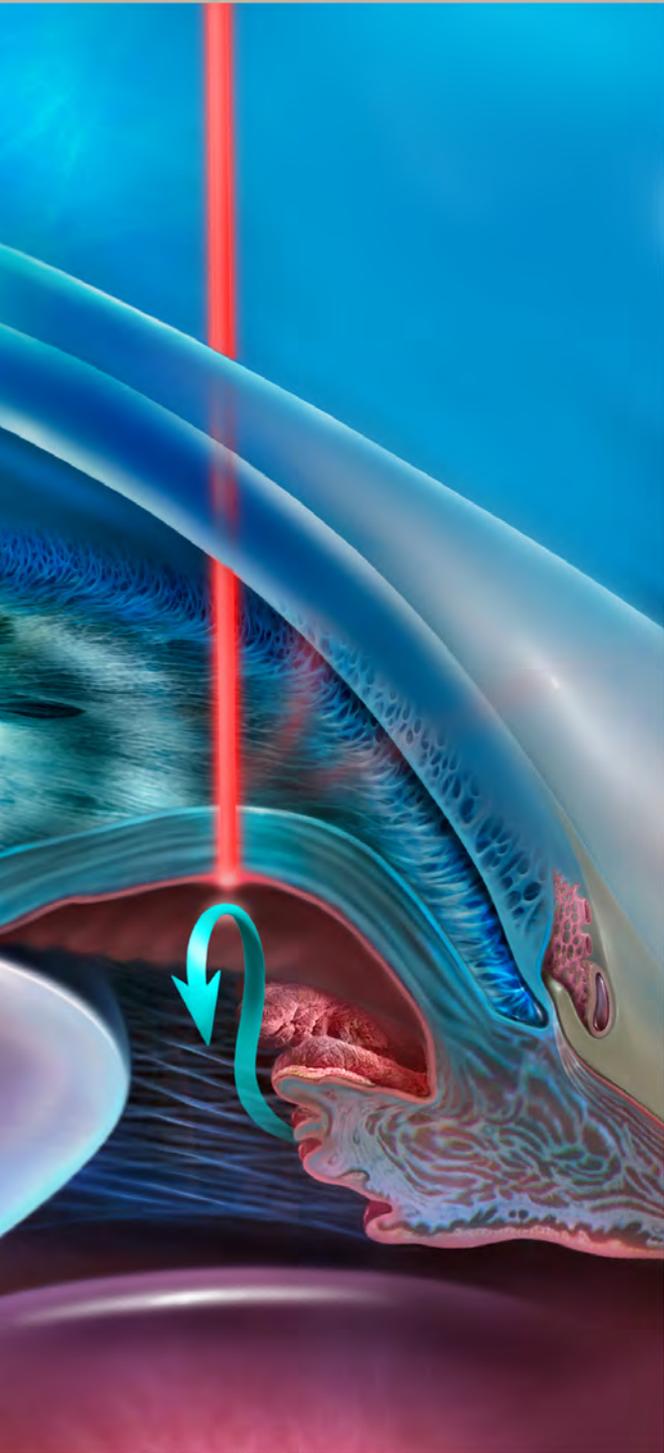
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ZAP, LiGHT & SALT

Three recent studies
address long-standing questions in glaucoma,
and they may change your practice.

By Annie Stuart, Contributing Writer

Should prophylactic laser peripheral iridotomy (LPI) be used extensively for primary angle-closure suspects (PACS)? Are eye drops and selective laser trabeculoplasty (SLT) comparable first-line treatments for primary open-angle glaucoma or ocular hypertension? Is inflammation helpful or a hindrance after SLT?

In 2019, three glaucoma studies—ZAP, LiGHT, and SALT—addressed these very issues.¹⁻³ “We’re lucky to have some high-quality studies on questions that are hard to answer,” said Jo Ann A. Giaconi, MD, at the University of California, Los Angeles. “Whether simply confirming what we already thought to be true or exploring new areas, they’re very helpful,” added L. Jay Katz, MD, of the Wills Eye Glaucoma Service in Philadelphia.

ZAP: Prophylactic LPI for Primary Angle-Closure Suspects

In the early 1900s, researchers found that an iridectomy could relieve acute attacks of high pressure in eyes of patients with narrow-angle glaucoma, said David S. Friedman, MD, PhD, MPH, at Harvard Medical School in Boston. Ophthalmologists also performed this procedure in the fellow eye, which had a very high chance of getting an acute attack, he said.

Laser peripheral iridotomy. In the mid-1970s, LPI became the first-line treatment for primary angle-closure glaucoma. With the advent of laser, the risk-benefit ratio favored treatment over observation, so LPI also became a common treatment for patients with narrow angles, said H. George Tanaka, MD, at Vold Vision in Fayetteville, Arkansas. These primary angle-closure suspects have an increased risk of an acute attack but have healthy nerves, normal intraocular pressure (IOP), no peripheral anterior synechiae (PAS), and no other symptoms.

“We’re always balancing risks and benefits with patients,” said Dr. Katz. “What’s the worst-case scenario if you develop angle-closure glaucoma? Pretty awful.” On the other side of the coin, “What’s the worst-case scenario with an iridotomy? A little inflammation, bleeding, or corneal edema, usually temporary,” he said. Although less common, the main long-term problem is glare. “Out of an abundance of caution, we’ve been erring on the side of doing an LPI because you just never know,” said Dr. Giaconi, adding that the risk of angle-closure glaucoma is higher for patients who don’t follow up regularly.

Illustration © 2020 Cynthia Turner

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The downside of this approach? There have been no guidelines or clinical evidence to support using LPI for all primary angle-closure suspects, said Dr. Tanaka. “That’s why studies like ZAP are so important.”

ZAP study design. In this six-year, randomized controlled trial, bilateral PACS patients between 50 and 70 years old were enrolled at a tertiary specialized hospital in Guangzhou, China. Eligible patients received LPI in one randomly selected eye, with an untreated contralateral control.

The primary outcome was PAC disease, a composite of three different endpoints: an increase in IOP, PAS, or acute angle closure. “In untreated eyes, PAS was by far the most common,” said Dr. Friedman, a ZAP coauthor. “But PAS is a slow, benign process that doesn’t result in visual loss or affect the patient’s life if pressures remain normal.”

Fewer attacks than expected. This study reaffirmed that acute angle closure is less common in at-risk eyes than previously thought and that the rate of developing PAS and elevated IOP is relatively slow, said Dr. Giaconi.

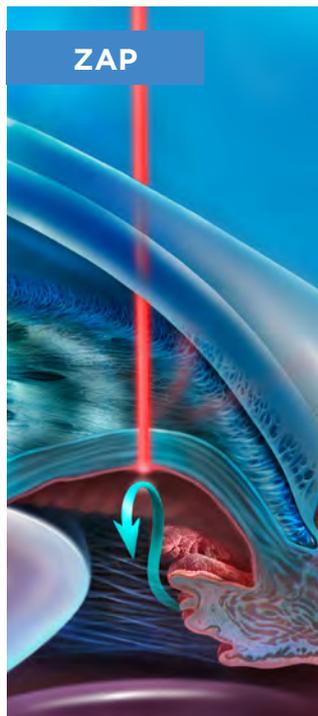
“Most attacks occurred after dilation,” said Dr. Friedman, “which was a part of our protocol to allow observation of any impact iridotomy had on the development of cataract. Without dilation, only two cases of acute attacks occurred in nearly 900 untreated eyes followed for six years.”

Older studies. “A similar earlier study reported nearly three times the rate of acute attacks,” said Dr. Friedman. “We based our sample size on the assumption of more events, which just didn’t happen.” Why the difference? One possible reason, said Dr. Giaconi, is that the ZAP study screened many patients in the community

instead of at tertiary clinics, where patients who show up may already have subtle signs and symptoms such as headache.

Another reason could be that past definitions of PACS and PAC have lacked precision, said Dr. Tanaka. And studies have used different criteria for occlusion, measured by gonioscopy, a somewhat subjective assessment resulting in variations in grading, added Dr. Katz.

Risk-benefit ratio: a new view. This study revealed that you needed to treat 44 PACS patients



When to Do LPI

Consider LPI in patients who have the following:

- symptoms such as headaches or eye pain that suggest the onset of primary angle closure,
- a family history of angle closure,
- signs such as PAS, high IOP, or an anterior lens surface that vaults into the anterior chamber.

Or those who may need dilated exams for diabetes and/or may not follow up or may travel to remote areas.

to prevent one case of primary angle closure in six years, said David Garway-Heath, MD, MBBS, FRCOphth, at Moorfields Eye Hospital in London. “One would imagine you’d need to treat even more to prevent one significant case of visual loss as a consequence of primary angle closure.”

The conversion rate was much lower than previously reported, said Dr. Tanaka. “This really supports the notion that observing low-risk primary angle-closure suspects is usually fine. Conversely, treating all primary angle-closure suspects with laser iridotomy is definitely overtreatment.”

LPI risks. As for LPI risks, the findings were mostly confirmatory, said Dr. Giaconi. In addition to assessing the more common side effects, the researchers also specifically looked at the endothelial cell count of the cornea, which didn’t change, said Dr. Friedman. The study also didn’t find an increased risk for cataract progression, but at least one other study⁴ has, said Dr. Tanaka, who has also seen this in his practice.

Study strengths and limitations. Dr. Giaconi called ZAP a very strong study, but she would have liked to see data on the measurement of lens vault, which is a risk factor for pupillary block and acute angle attacks in other Asian studies. Overall, she said, “The researchers really thought about their inclusion and exclusion criteria and how to gather data.” The study also verified endpoints with a second observer, said Dr. Friedman.

Dr. Tanaka pointed to three major strengths of the study: 1) Each patient served as his or her own control. 2) Follow-up was six years—extended to recruit more patients because the number of endpoints met at three years was so low. 3) All patients essentially received a provocative test: dilation.

The main limitation of the study is the inability to generalize results to other populations. “Angle closure in China may not be the same as in the United States, for example,” said Dr. Katz, citing

different demographics and eye anatomies, and potentially different mechanisms of action. On the plus side, Dr. Friedman doesn't think the rates would be higher elsewhere. That's because Chinese have among the highest rates of acute attacks.

"Along with others in the United Kingdom, the Working Group for the Royal College of Ophthalmologists will make recommendations for how to implement the results of this study in our population," said Prof. Garway-Heath. And the Academy's updated *Preferred Practice Patterns* for glaucoma are expected to be published in early 2021.

Practice implications? "ZAP has made me think that I don't want to search for angle-closure suspects because I'm not sure we benefit tremendously by finding them," said Dr. Friedman. "From a public health standpoint, I think we should change what we are doing."

Dr. Katz agrees that the public health message is clear, and that it's reassuring most people will be fine, even if never diagnosed. "But I'm a physician, and once I have a patient with a narrow angle in front of me, it's my obligation to describe the risks, options, warning signs of acute angle closure, and need for follow-up. Then it's the patient's right to decide what to do."

However, this study makes it easier to reassure primary angle-closure suspects that observation is often a reasonable approach, said Dr. Tanaka.

"If you don't have LPI, your actual risk of an acute attack is on the order of 1% or less over six years." Dr. Tanaka would only recommend a laser iridotomy in a subset of patients, specifically those who:

- have symptoms such as headaches or eye pain that suggest the onset of primary angle closure,
- have a family history of angle closure,
- may need dilated exams for diabetes, and/or
- may not follow up or may travel to remote areas.

In addition, Dr. Giaconi recommends an iridotomy for patients with signs such as PAS, high IOP, or an anterior lens surface that vaults into the anterior chamber.

LiGHT: SLT or Eyedrops as First-Line Treatment

In 1990, the multicenter, NEI-funded Glaucoma Laser Trial evaluated argon laser trabeculoplasty (ALT), a predecessor to selective laser trabeculoplasty (SLT).⁵ "The large study showed that it [ALT] was equally, if not more, effective than timolol in controlling the pressure in patients with glaucoma," said Dr. Katz, "but it never really changed our practice."

Smaller trials leading up to LiGHT showed similar results with SLT: It worked as well as lat-

anoprost as a first-line therapy to lower pressure with minimal side effects, he said. But still there was little movement away from drops. "About 15 years ago, our Medicare billing study⁶ showed that SLT was being done in less than 5% of people with glaucoma," said Dr. Friedman.

An eyedrops bias? Why the continued reluctance to use SLT? There are likely many contributors, ranging from provider inertia to patient fears and misconceptions. "When you say 'laser' to patients, it can conjure up James Bond being cut in half," said Prof. Garway-Heath. "Some clinicians also refer to laser as surgery. We tend not to in the United Kingdom, lumping it in with medical, rather than surgical, treatment."

Although the literature has made a fairly compelling case for laser trabeculoplasty as a first-line treatment, Prof. Garway-Heath said it's often been reserved as an add-on treatment in patients who have IOP that's been difficult to control with medication. "And in general, add-on treatments are less effective than primary treatments," he said, indicating that this may be an important reason laser has been perceived as having low efficacy in the real world.

Not only is SLT less effective when used as an add-on treatment, said Dr. Katz, but these patients are more likely to experience pressure spikes, inflammation, and other problems. "These are people who are already hanging onto the cliff with their fingernails," he said. "Zapping them with laser might push them over the edge."

LiGHT study design. With help from patients, LiGHT compared SLT with latanoprost eyedrops as first-line treatments for ocular hypertension and glaucoma. "In the United Kingdom, we involve patients in the design of studies and ask them about their outcomes of interest," said Prof. Garway-Heath, a LiGHT coauthor. "The advice we get from patients is very helpful."

Before conducting the LiGHT study, patients told the researchers that being drop free was important to them, he said. This helped the researchers craft a different kind of study than had been done in the past, one where the main outcomes were related to patient quality-of-life (QoL) measures and cost effectiveness; an important out-



come was achieving target pressures without the need for eyedrops.

Efficacy and safety of SLT. “This study confirmed what we knew from our clinical experience—that SLT is about as effective as one drop of latanoprost,” said Dr. Tanaka. “I have offered it as a first-line treatment for a while, even before studies like LiGHT.” Although the study also reaffirmed Dr. Giacconi’s thinking and approach, the side effects of SLT were fewer and the benefits greater than she’d previously described for her patients.

“In the LiGHT trial, lack of compliance might account for the higher rate of progression in the medically treated patients,” said Dr. Tanaka.

“Based on some studies, compliance rates at best may be 50% with a once-a-day drop. If you add a second drop, compliance goes down even further.”

Based on previous literature, Prof. Garway-Heath was also not surprised by the efficacy and safety of the laser. “However, I was a little disappointed that we didn’t see more on the quality-of-life outcomes, which all slightly favored the laser but were not statistically significant,” he said. “The larger differences were, as expected, with the ocular surface questionnaire. The main QoL outcome was chosen to allow the calculation of quality-adjusted life years, but it is a fairly blunt QoL instrument.”

ZAP, LiGHT, and SALT

	Participants	Length	Outcomes	Results
ZAP	889 primary angle-closure suspects Contralateral eyes as controls	72 months	Primary angle closure disease as a composite endpoint of increased IOP, PAS, or acute angle closure	A primary outcome event occurred in: • 19 treated eyes • 36 untreated eyes No serious adverse events
LiGHT	718 participants with: • 356 in the SLT group • 362 in the eyedrops group	36 months	Primary outcome: HRQoL assessed by EQ-5D Secondary outcome: • Cost and cost-effectiveness • Disease-specific HRQoL • Clinical effectiveness • Safety	Primary outcome: No significant difference between the two groups Secondary outcome: • 97% probability of SLT as first treatment being more cost-effective than eyedrops • 74.2% in SLT group required no drops to maintain IOP at target • Eyes in SLT group were within IOP targets at more visits than eye in eyedrops group • Surgery required in 11 of eyedrops group vs. zero in SLT group
SALT	96 eyes of 85 individuals randomized to one of three groups before SLT: ketorolac 0.5%, prednisolone 1%, or saline. Drops were used 4x/day for five days, starting the day of SLT.	12 weeks	Primary outcome: IOP at 12 week Secondary outcome: • IOP at 1 and 6 weeks • Patient-reported pain • Detectable anterior chamber inflammation	Primary outcome: Statistically significant decrease in IOP in both steroid and NSAIDs groups compared to placebo Secondary outcome: No statistically significant differences between groups: • In IOP at 6 weeks • In discomfort at 1 hour and 1 week • In inflammation at 1 hour and weeks 1, 6, and 12

EQ-5D: EuroQOL-5D; **HRQoL:** Health-related quality of life.

Cost-effectiveness of drops versus laser. “Given that we were expecting more or less equivalence between the two types of treatment in effectiveness, the superiority in SLT’s cost-effectiveness really stood out,” said Prof. Garway-Heath. However, Dr. Tanaka would expect an even larger difference in the United States because patient co-pays and deductibles can be high. If the laser doesn’t have longevity, it won’t save much, said Dr. Tanaka. But if bilateral SLT lasts four years, that’s the equivalent of nearly 3,000 drops of medication.

Repeat treatments. “In LiGHT, repeated treatment ended up working in a lot of people,” said Dr. Friedman, adding that his past practice has been to stop if the laser didn’t work the first time. “I will now likely change my algorithm and try again after six to eight weeks if it doesn’t work the first time.” In LiGHT, the second treatment actually lowered pressures relatively more than the first treatment, Dr. Giaconi pointed out.

Unlike its predecessor, SLT seems to be much more amenable to repeat treatment, said Dr. Katz. This study had a defined protocol of treating 360 degrees, but in the “real world,” practices may vary, making it harder to know exactly how effective retreatment will be and for how long.

Study strengths and limitations. “Funded by the U.K.’s National Institute for Health Research, LiGHT was a large, well monitored, and very well implemented study—pretty definitive,” said Dr. Friedman.

Dr. Tanaka pointed out one caveat. “The protocol doesn’t reflect what U.S. ophthalmologists do in real life,” he said. In the laser arm, patients received laser and a second laser if the first didn’t work. If that was unsuccessful, patients were put on drops and received surgery if drops didn’t control pressures. In the eyedrops arm, doctors immediately offered patients surgery if medical treatment failed.

“In the United States, we offer patients laser before surgery if they choose not to use eyedrops or if eyedrops fail,” said Dr. Tanaka. “This has been the traditional paradigm for 20 years.” The LiGHT protocol largely explains why 11 patients in the medically treated group needed surgery, he said. If they had been offered laser before surgery, this number might be lower.

Change practice? “Like many other ophthalmologists, I often didn’t think of laser as part of the first-line treatment conversation,” said Prof. Garway-Heath. “Now I do. It’s routine for me to tell patients that they have three options—either to be observed, have laser, or have drops.”

If you are a public health official, the results of the study would suggest laser for everybody with early-to-moderate open-angle glaucoma, said Dr.

Katz, and the addition of medications and other surgery as needed. “But talking to an individual is different than looking at this from a public health perspective,” he said, adding that he doesn’t like to push patients against the wall. However, the study does help with these conversations. “I feel more confident telling patients that we have a study strongly supporting laser as a first-line therapy.”

Dr. Giaconi agrees, and she uses the study results to reassure patients not only about laser’s efficacy, but also its safety. “I explain that it rejuvenates the drain, like laser rejuvenates the skin.” She also works in a VA glaucoma clinic, where SLT is often used as a last step before surgery. “I shared this paper with our residents and optometry service,” she said, explaining that it often makes sense to refer patients for SLT, rather than prescribing drops and holding on to patients.

SALT: Improving SLT Outcomes With Anti-Inflammatories

SLT is relatively benign, said Dr. Tanaka. However, using more energy with certain patients, such as those with less pigment in the angle, can cause photophobia or discomfort in the hours or days after the laser—which can be bothersome in some people, he noted.

“Because they don’t want to get the phone call, some physicians automatically put SLT patients on steroids or NSAIDs after SLT,” said Dr. Tanaka. Others have been concerned that reducing the postlaser inflammatory response might lessen the efficacy of the laser, interfering in some way with its mechanism of action. “Nobody knew who was right,” said Dr. Tanaka.

Results of the study. The purpose of SALT was to examine whether short-term topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) after SLT could improve its efficacy.

In fact, patients in this study who used steroids or NSAIDs did better at three months than those who did not. Compared with placebo, the steroid group had a 2 mm Hg IOP decrease, and the NSAID group had a more than 3 mm Hg IOP decrease. Dr. Tanaka found it striking that immediate postoperative treatment given only four times a day for four days could produce such a



large effect at 12 weeks. There was no difference in response at six weeks. A blunting of the inflammatory response might explain why, said Dr. Tanaka.

Study limitations and strengths. “SALT is the sort of study that is indicative, rather than definitive,” said Prof. Garway-Heath. “It is quite small with only about 30 patients per group. And, even though it was randomized, there was quite a difference in the number of eyes treated—28 in the NSAIDs group and 37 in the steroid group.”

Because it was left up to the clinician, there were also fairly large differences between the groups in the intensity of treatment given, he said. “In the NSAIDs group, only 25% had a 180-degree treatment and in the saline group, it was 45%,” said Prof. Garway-Heath. “This might partly explain pressure differences.”

This study also had a limited follow-up period. However, Prof. Garway-Heath said that the LiGHT study found two-month post-treatment pressures were a good indicator of future pressure control, suggesting that ophthalmologists should not automatically dismiss the 12-week results in SALT.

Time to change practice? Professor Garway-Heath and Dr. Katz aren’t quite there yet. “I think this is good evidence but not sufficient to change practice,” said Prof. Garway-Heath. Dr. Katz also has concerns about the size and length of the study, as well as questions about how clini-

cians’ different laser practices—number of shots, amount of energy, or degree of treatment—might produce different outcomes.

On the other hand, Drs. Friedman, Tanaka, and Giaconi are less circumspect. “A short course of medication after SLT is not risky,” said Dr. Giaconi, “and it is beneficial if it gains patients a few extra millimeters of mercury.”

Dr. Friedman found the effect “a little biologically hard to believe. “But does it influence how I will behave?” he asked. “Yes. In my view, providing a steroid or NSAID is probably the better decision. Given the strong findings in favor of treatment, it is unlikely that a second study will show that treatment adversely affects the procedure.”

Dr. Tanaka is also reassured. “This shows us that we can treat patients for comfort following a pretty benign procedure and not worry it will limit its effectiveness,” he said. “It works hand in hand with LiGHT: Be generous in offering patients laser and afterward, feel free to give an anti-inflammatory.”

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MEET THE EXPERTS

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MPH Chair and director of glaucoma and medical director for clinical research at Massachusetts Eye and Ear and codirector of the Glaucoma Center of Excellence at Harvard Medical School, in Boston. *Relevant financial disclosures: None.*

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AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Foundation

Attend the Reimagined Orbital Gala, Now Virtual

Our 17th annual fundraiser will be the most exciting social event of AAO 2020 Virtual — a fast-paced revelry complete with drinks and appetizers (bartender and chef not included), some laugh-inducing entertainment, and of course, a gripping auction. Plan now to join your colleagues from around the globe. Proceeds benefit the Truhlsen-Marmor Museum of the Eye.

**Watch for updates at
aao.org/gala**

Orbital Gala 2020

On a Screen Near You
Saturday, Nov. 14
5 p.m. PST



Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Rx Only

BRIEF SUMMARY

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DO dosage AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Pigmentation

Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the effects of increased pigmentation are not known.

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

Eyelash Changes

Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

Rocklatan® contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because it may exacerbate inflammation...

Macular Edema

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

Herpetic Keratitis

Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

Bacterial Keratitis

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

Use with Contact Lenses

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

ADVERSE REACTIONS

Clinical Trials Experience

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

Rocklatan®

The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

Netarsudil 0.02%

Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%

Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS

Although specific drug interaction studies have not been conducted with Rocklatan®, *in vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution 0.005%. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on netarsudil ophthalmic solution use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥ 0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥ 3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

For latanoprost, in 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

Lactation

There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. It is also not known whether latanoprost or its metabolites are excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rocklatan® and any potential adverse effects on the breastfed child from netarsudil and latanoprost.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

For additional information, refer to the full prescribing information at www.Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.



Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

Rocklatan® is a registered trademark of Aerie Pharmaceuticals, Inc.
U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,931,336; 9,993,470



Superior efficacy. Optimal simplicity.^{1,2}

Once-daily Rocklatan[®] significantly lowers IOP in patients with open-angle glaucoma or ocular hypertension—superior to latanoprost and netarsudil at every measured timepoint in phase 3 clinical trials.^{1,2}

The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor



Nearly 60% of Rocklatan[®] patients achieved a target pressure of 16 mmHg or less²



The majority of ocular adverse events were mild and tolerable, with minimal systemic adverse events^{1,3}



Once-daily dosing relieves treatment burden and may improve adherence and treatment outcomes^{1,4}

IOP: intraocular pressure; ROCK: rho kinase



Visit Rocklatan.com to learn more about this innovative drop for elevated IOP

IMPORTANT SAFETY INFORMATION

Contraindications

None.

Warnings and Precautions

- Pigmentation changes
- Eyelash changes
- Intraocular inflammation
- Macular edema
- Herpetic keratitis
- Bacterial keratitis
- Contact lens wear

Adverse reactions

Rocklatan[®]: The most common ocular adverse reaction is conjunctival hyperemia (59%). Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Netarsudil 0.02%: Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%: Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reaction.

Please see brief summary on the adjacent page.

For full Prescribing Information, please visit Rocklatan.com.

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INDICATIONS AND USAGE

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References:

1. Rocklatan[®] (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Prescribing Information, Aerie Pharmaceuticals, Inc., Irvine, Calif. 2019.
2. Asrani S, McKee H, Scott B, et al. Pooled phase 3 efficacy analysis of a once-daily fixed-dose combination of netarsudil 0.02% and latanoprost 0.005% in ocular hypertension and open-angle glaucoma. Presented at the 13th Biennial Meeting of the European Glaucoma Society, March 2018.
3. Data on file. Aerie Pharmaceuticals, LLC.
4. Prum B Jr, Rosenberg L, Gedde S, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern guidelines. *Ophthalmology*. 2016;123(1):P41-P111.