Special Report

TAKING NEW CLUES FROM EXFOLIATION SYNDROME INSIGHT

EXFOLIATION syndrome was first described 100 years ago, but its importance was largely ignored for the first 90 of those years, said Robert Ritch, MD. Glaucoma is an ocular manifestation of this systemic disease with distinct mechanisms. By understanding these mechanisms, clinicians could potentially identify non-IOP-lowering treatment modalities that are applicable at various steps of disease development.

(See story on page 13: Exfoliation)

Clinical Diagnosis

IT TAKES A VILLAGE: VISION SCREENING COLLABORATION

ONE PEDIATRIC ophthalmologist has spent 30 years educating the Louisiana community’s stakeholders about the importance of vision screening for young children. Alan B. Richards, MD, shares how his work has been effective through a grassroots and collaborative approach.

(See story on page 31: Vision screening)

By Cheryl Guttman Krader;
Reviewed by Carl Regillo, MD

RANIBIZUMAB 100 mg/mL delivered via the port delivery system (PDS) (Genentech) holds promise for providing safe and effective durable control of neovascular age-related macular degeneration (nAMD) in patients with anti-VEGF responsive disease, according to results of the LADDER study.

The phase II clinical trial was designed to characterize the durability and safety of the device. The durability results were very promising and exceeded expectations, and the safety profile looked good, especially after introducing modifications to the surgical technique, said Carl D. Regillo, MD, study investigator, and chief of the Retina Service, Wills Eye Hospital, Philadelphia.

“The techniques for device implantation and refilling are unique, but with training and meticulous care, they can be readily and safely adopted by vitreoretinal surgeons,” Dr. Regillo added.

In LADDER, 220 patients were randomly assigned 3:3:3:2 to treatment with PDS 10, 40, or 100 mg/mL or intravitreal ranibizumab 0.5 mg (Lucentis, Genentech). The PDS—a scleral-based intravitreal reservoir releasing ranibizumab via passive diffusion—was refilled as needed based on protocol-defined criteria.

(Continues on page 27: LADDER)

Decreasing burden of nAMD therapy

Investigators optimistic about sustained-release ranibizumab delivery based on phase II LADDER study

VIDEO ANIMATION: Go to OphthalmologyTimes.com/Refillable

By Cheryl Guttman Krader;
Reviewed by Carl Regillo, MD

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(Continues on page 27: LADDER)
CONFIDENCE IN PLACEMENT LEADS TO CONFIDENCE IN OUTCOMES

Combining trabecular bypass technology with the additional benefits of open-window scaffolding and a 90° span of Schlemm’s canal, the Hydrus® Microstent’s Tri-Modal™ mechanism of action provides confidence in both placement and outcomes for patients with mild to moderate primary open-angle glaucoma.

Delivering a new confidence.
Surgery

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How a novel classification system could replace the Amsler-Krumeich Classification.

Special Report

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Ask yourself: ‘What is the anatomy giving me?’ to help decide the most effective procedure.

Clinical Diagnosis

32 DON'T OVERLOOK PREOPERATIVE OSD
Follow an ocular surface disease protocol for the most favorable cataract outcomes.

What's Trending

See what the ophthalmic community is reading on OphthalmologyTimes.com

1 Top ophthalmic challenges for 2019
http://bit.ly/2s42lyx

2 Dr. Mali's top 5 stories in ophthalmology for 2018
http://bit.ly/2zWsZO2

3 Ophthalmic year in review

4 Branded versus generics: You make the call
http://bit.ly/2D0QRlr

ICYMI: Watch Patrik De Haes, MD, CEO of Oxurion NV, share the latest updates in clinical studies at the 2018 OIS@AAO meeting in Chicago

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A renewed vision
How an unforgettable patient could see—and speak out—again

By Peter J. McDonnell, MD

editorial

By Peter J. McDonnell, MD
director of the Wilmer Eye Institute,
Johns Hopkins University School of
Medicine, Baltimore, and chief medical
editor of Ophthalmology Times.

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E-mail: pmcdonn1@jhmi.edu

LIKE ALL OF MY fellow earthlings, I
live in a country with many flawed political
leaders. Unlike a large percentage of those who
share my planet, however, I live in a country
in which I feel free to express my dissatisfac-
tion with those rascals.

Many countries forbid criticism or insults
directed at their leaders, through formal laws
or informal sanctions (“Care for a little more
polonium in your tea, sir?”). People in my
country of birth are even legally permitted to
burn our flag if they care to do so, although I
will be prosecuted and fined if I burn a pile of
leaves that I raked in my backyard.

All of which brings to mind a patient from
years ago. I was a young assistant professor and
he, a healthy-appearing man in his early 70s,
was brought to see me by his son and daughter.

CATARACT DIAGNOSIS ON
TOP OF ALZHEIMER’S

Their father, they explained, was diagnosed
two years previously with Alzheimer’s dis-
ease. He had 24-hour nursing care, seemed
outwardly happy but had severe dementia, and
a judge had appointed the two children as his
legal guardians.

The son and daughter and his nurses could
tell that the father no longer could see. He had
a history of dense amblyopia in one eye, but
had previously enjoyed excellent sight in his
other “good” eye.

But for the last year, he seemed not to see.
He would sit all day and listen to a radio, but
not show any interest in reading or looking at
things and didn’t get up to walk without some-
one guiding him. His local ophthalmologist di-
agnosed cataract and recommended they bring
their functionally one-eyed father to see me.

My examination showed advanced brunes-
cent cataracts but otherwise apparently healthy
eyes. The man could not read the eye chart, but
clearly had some low level of visual function.

The son, daughter, and I discussed the situ-
ation at length while their father sat childlike
in the exam chair, seemingly unable to pay any
attention. I explained why we are generally
reluctant to proceed with surgery in patients
with comorbidities that might keep them from
experiencing an improved quality of life. Also,
his severe dementia would mean that he would
need general anesthesia.

The son and daughter strongly wished to
take the chance to improve their father’s vision,
and a week later he had the surgery. Every-
thing went well and I saw him once postopera-
tively. Because it was hard to transport their fa-
ther the long distance to see me, they arranged
for their local ophthalmologist to check him af-
fterward. I never saw him again.

Two years later, I received a letter in the
mail. The son and daughter had written to let
me know that their father had died.

A HAPPIER LIFE

They described how during the weeks and
months after the surgery, their father progres-
sively interacted more and more with them
and others. He began reading the newspaper
again every morning and discussed with them
what he had read.

“When he began to complain bitterly about
the idiotic decisions being made by the govern-
ment, we realized that you had given our father
back to us for the last two years of his life,”
they wrote.

I have always been grateful that my patient’s
children took the time to let me know what
happened to their father.

Plus, it drove home to me that for at least
some of us Americans, being fully human in-
cludes our exercising our fundamental right to
remonstrate about our politicians.
XIIDRA MAY INTERRUPT
THE CYCLE OF INFLAMMATION
CENTRAL TO DRY EYE DISEASE\textsuperscript{1,2}

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.\textsuperscript{1}

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**Indication**

Xiidra\textsuperscript{TM} (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

**Important Safety Information**

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

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

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

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

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

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

**References:**


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BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

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

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

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

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1,401 patients received at least 1 dose of lifitegrast (1,287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

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

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

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. An in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5,400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
Keratoconus progression: Looking beyond Kmax
CXL has potential to alter disease course; progression display plays role in when to intervene

By Michael W. Belin, MD; Special to Ophthalmology Times

Corneal collagen crosslinking (CXL) offers the opportunity to slow, stabilize, or even partially reverse what has been a chronically progressive disease in keratoconus. Though CXL has been available for more than a decade outside the United States, its usage within America is still, to some degree, in its infancy.

Adaption of this treatment modality has been hampered by both the expense and the lack of appropriate insurance coverage. When covered, however, many insurance carriers require documentation of further progression using the parameters from the FDA CXL trials. The most commonly used progression parameter is an increase in Kmax of 1 D or more.

Parameters used in FDA trials are just that, and are not meant to set or establish a standard of care, let alone used limit access to care.

An abnormal anterior surface with an elevated Kmax already implies some degree of visual compromise. A further increase in Kmax, as required by many carriers, is typically associated with a further reduction in visual function. This is contrary to our normal practice of medicine. When we identify a patient with elevated serum cholesterol levels, we empirically start the patient on a statin. We do not wait until they have an occlusive event.

Yet, frequently, our current approach to keratoconus is to intervene only after the patient has already lost vision. This is secondary to both a late diagnosis and the mandate that anterior surface parameters, such as Kmax, must change before carriers will cover the cost of CXL.

A few years ago, we introduced a new classification system (Table 1) on the OCULUS Pentacam, the Belin ABCD Keratoconus Staging, to replace the grossly outdated, but commonly used, Amsler-Krumeich Classification. The benefit of the new system was its recognition of both corneal surfaces and readings centered on the thinnest point of the cornea, as opposed to apical readings that have been used in the past.

The ABCD classification uses the anterior (A) and posterior (B for back) radius of curvature taken from a 3-mm optical zone centered on the thinnest point, the thinnest corneal thickness (C), and distance visual acuity (D) (Table 1).

The same parameters can be used to determine when statistically significant progression occurs.

### Table 1

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ARC (3 MM ZONE)</th>
<th>PRC (3 MM ZONE)</th>
<th>THINNEST PACHYMETRY</th>
<th>BEST SPECTACLE DISTANCE VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>&gt; 7.25 mm (&lt; 46.5 D)</td>
<td>&gt; 5.90 mm</td>
<td>&gt; 490 μm</td>
<td>≥ 20/20 (≥1.0)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>&gt; 7.05 mm (&lt; 48.0 D)</td>
<td>&gt; 5.70 mm</td>
<td>&gt; 450 μm</td>
<td>&lt; 20/20 (&lt; 1.0)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>&gt; 6.35 mm (&lt; 53.0 D)</td>
<td>&gt; 5.15 mm</td>
<td>&gt; 400 μm</td>
<td>&lt; 20/40 (&lt; 0.5)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&gt; 6.15 mm (&lt; 55.0 D)</td>
<td>&gt; 4.95 mm</td>
<td>&gt; 300 μm</td>
<td>&lt; 20/100 (&lt;0.2)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&lt; 6.15 mm (&gt; 55.0 D)</td>
<td>&lt; 4.95 mm</td>
<td>≤ 300 μm</td>
<td>&lt; 20/400 (&lt; 0.05)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>STANDARD DEVIATION</th>
<th>80% 1-TAIL CONFIDENCE INTERVAL</th>
<th>95% 1-TAIL CONFIDENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoconus ARC (n = 252)</td>
<td>0.062 mm</td>
<td>0.052 mm</td>
<td>0.102 mm</td>
</tr>
<tr>
<td>Normal ARC (n = 135)</td>
<td>0.015 mm</td>
<td>0.012 mm</td>
<td>0.024 mm</td>
</tr>
<tr>
<td>Keratoconus PRC</td>
<td>0.062 mm</td>
<td>0.052 mm</td>
<td>0.102 mm</td>
</tr>
<tr>
<td>Normal PRC</td>
<td>0.050 mm</td>
<td>0.042 mm</td>
<td>0.083 mm</td>
</tr>
<tr>
<td>Keratoconus Minimum Pachymetry</td>
<td>6.03 μm</td>
<td>5.07 μm</td>
<td>9.92 μm</td>
</tr>
<tr>
<td>Normal Minimum Pachymetry</td>
<td>4.79 μm</td>
<td>4.03 μm</td>
<td>7.88 μm</td>
</tr>
</tbody>
</table>
To use these parameters to determine progression, we first had to determine the measurement noise levels associated with each parameter.

One-sided confidence intervals were calculated using both a normal and keratoconic population. It was important to measure both populations since very early or subclinical disease more likely mimics the normal population noise, while more advanced disease with anterior surface changes should more closely follow the keratoconic population. One-sided confidence intervals at both the 80% and 95% levels were determined (Table 2 on Page 8).

The Belin ABCD Progression Display graphically displays the three machine-generated parameters (A, B, and C) and the single-user entered D parameter over time.

In addition, it displays in tabular format at the bottom of the display 11 supplementary parameters including: ABCD classification, overall BAD reading, progression index, ARTmax, Kmax, Q values, ISV, IVA, IHA, and IHD.

Up to 8 individual exams can be displayed. The baseline exam defaults to the oldest exam, but any exam can be set as baseline for comparison purposes by the operator. Treatment date is user selected and displayed by the horizontal hatched line.

The confidence intervals representing statistically significant change at both the 80% and 95% levels are shown in green generated from the normal population and in red generated from the keratoconic population. The confidence intervals are not displayed post-treatment date (Figure 1 on Page 10).

The ABCD parameters may be graphically displayed in two different scaling formats. “Aligned at Baseline” is the default option. With this scaling option all the baseline parameters are aligned (upper display, Figure 2 on Page 10). The benefit of this scaling is that it increases the separation of the confidence interval markers making it somewhat easier to visually determine progression, but you lose the relative ABCD grading.

The other option “Full Scale” maintains the relative ABCD classification scaling (bottom display, Figure 2 on Page 10), but the confidence interval markers are more condensed. There is also a magnification tool that will allow easier visual determination if needed.

**RIGHT TIME TO INTERVENE?**

Keratoconus is a progressive disease with serious and often irreversible visual sequelae. Past treatments were for late disease and typically never returned the patient to normal visual function.

CXL has the potential to alter the natural course of the disease and, if implemented early enough in the disease process, to prevent visual loss. Past diagnostic criteria and progression determinants were inadequate to identify the disease and its progression in the earliest stages.

The Belin ABCD Progression Display can provide additional information to assist both the surgeon and patient in determining the proper time to intervene.
The clinical utility of the ABCD Progression Display can be seen in the clinical examples here (from page 9).

**FIGURE 1** The confidence intervals representing statistically significant change at both the 80% and 95% levels are shown in green generated from the normal population and in red generated from the keratoconic population. (All tables and images courtesy of Michael W. Belin, MD)

**FIGURE 2** The ABCD parameters may be graphically displayed in two different scaling formats. “Aligned at Baseline” is the default option. With this scaling option all the baseline parameters are aligned (upper display). The other option “Full Scale” maintains the relative ABCD classification scaling (bottom display), but the confidence interval markers are more condensed.

**FIGURE 3** An asymptomatic 15-year-old with very early ectatic change (final “D” from the BAD < 3.0) on initial presentation and initial Kmax of 46.1 with follow-up exams at 5 and 13 months. The patient remains asymptomatic with subsequent Kmax readings of 45.5 and 45.8 (no change). The ABCD progression display, however, clearly demonstrates highly significant change on the posterior surface in spite of a stable anterior surface. The need for CXL could be demonstrated here prior to any visual loss.

**FIGURE 4** An 18-year-old with moderately advanced keratoconus (final “D” from BAD > 7.0) has 4 sequential exams over a 14-month period. There is no significant change on the anterior surface and initial Kmax values of 51.2. Subsequent exams do not show a change in Kmax ≥ 1 D though the progression display clearly documents significant change on both the posterior surface and minimal corneal thickness.

**FIGURE 5** A 16-year-old with early subclinical disease (final “D” from BAD < 3.0) who was lost to follow-up and returns after 15 months with highly significant change on all the ABC parameters (all beyond the 95% confidence interval) in spite of the fact that Kmax shows less than a 1 D variance.

**PROGRESSION**

(Continued from page 9)

References


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Dr. Belin is professor of ophthalmology and vision science, University of Arizona, Tucson. He serves as a consultant to Avedro, CXLO, and OCLUS Optikgeräte GmbH.
INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

• Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent.
• Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation.
• Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation.
• Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

IMPORTANT SAFETY INFORMATION (CONTINUED)

• There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients.
• Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration.
• Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%).

For more information, please see Brief Summary of Prescribing Information on next page.

References:

2. Weinreb RN, Stifflini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLO study. Ophthalmology. 2016;123(5):965-973.

For more information about VYZULTA and how it works, visit vyzultanow.com.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE
VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Pigmentation
VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmentation.

5.2 Eyelash Changes
VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes should not be considered irreversible, because discontinuation of treatment may lead to the return of normal eyelash and vellus hair growth.

5.3 Intraocular Inflammation
VYZULTA should be used cautiously in patients with a history of intraocular inflammation (iritis/uveitis) and should not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in patients with a history of macular edema, or in patients with cystoid macular edema.

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

5.6 Use with Contact Lens
Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS
The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.8% of patients discontinued therapy due to ocular adverse reactions including conjunctival hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 μg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternal and vertebral skeletal anomalies, limb hypertension and malformation, abdominal distention and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) [see Data]. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, 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
Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose) to a body surface area basis, assuming 100% absorption. Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 0.6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, fused fontanelles, and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses > 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hypoplasia and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

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

8.4 Pediatric Use
Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the in vivo rat bone marrow micronucleus assay. Chromosomal aberrations were observed in vitro with human lymphocytes in the absence of metabolic activation. Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime studies, did not cause any evident clinical symptoms.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology
A 9-month toxicity study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per eye, bid. The systemic exposure, on an equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC Bridgeville, NJ 08007 USA U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467. VYZULTA is a trademark of Bausch & Lomb Incorporated or its affiliates. © Bausch & Lomb Incorporated Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017
logic mechanisms leading to dysfunction of the trabecular meshwork, according to Dr. Ritch. “By understanding these mechanisms, we could potentially identify non-IOP-lowering treatment modalities that are applicable at various steps of disease development,” he said.

CURRENT KNOWLEDGE

To date, two single nucleotide polymorphisms (SNPs) in exon 1 of the \textit{LOXL1} gene have been associated with XFS and are thought to be present in up to 99% of affected Caucasians. On the flipside, however, not all people with the \textit{LOXL1} SNPs manifest XFS (at least in the eye).

“\textit{LOXL1} is a member of the family of lysyl oxidase enzymes that catalyze crosslinking of elastin and collagen, and they are essential for the formation and maintenance of elastic fibers and extracellular matrix homeostasis,” Dr. Ritch explained.

In addition, a genome-wide association study conducted in Singapore has discovered six additional genes associated with XFS and one rare allele that protects against its development.

An infectious origin has been postulated. This idea stems from the finding that younger people who undergo penetrating keratoplasty using graft tissue from an older donor can develop XFS earlier than its typical onset. The suggestion has also been made that XFS may be a slow prion disorder.

First insights on the cellular mechanism un-
derlying XFS are available from a study conducted by Dr. Ritch and colleagues Andrew Want, PhD, Audrey Bernstein, PhD, and J. Mario Wolosin, PhD.

Comparing tenon fibroblasts from patients with XFS with those from age-matched patients with primary open-angle glaucoma (POAG) or who had undergone strabismus surgery, the researchers suggested that XFS is a disease of dysfunctional autophagy.

“Normally, intracellular lysosomes travel on microtubules to the perinuclear area where their contents are degraded,” Dr. Ritch said. “In XFS, however, the microtubule organizing center is mislocalized such that lysosomes congregate at the cell periphery, apparently due to abnormal binding to microtubules, and mitochondria are depolarized.”

The decreased clearance of autophagosomes and a decreased ability to degrade misfolded proteins and aging organelles may underlie the development of extracellular protein aggregates in XFS, he added.

Dr. Ritch and colleagues also found that treatment with davunetide, a peptide that is being investigated in clinical trials for the management of various neurodegenerative diseases, stabilized the microtubules and allowed lysosomes to move to the perinuclear area.

Perhaps davunetide may also be a therapeutic option for XFS and one that could stop the pathophysiologic pathway leading to glaucoma,” Dr. Ritch said.

**Ocular and Systemic Associations**

While open-angle glaucoma is the most common ocular manifestation of XFS, this systemic disease has several other ocular associations.

They include angle-closure, cataract, zonulopathy, tear film disturbances, keratopathy, posterior synechiae, iris sphincter fibrosis, macular degeneration, and retinal vein occlusion. XFS is also associated with ischemia, impaired endothelial function, and impaired systemic vascular regulation, and a long list of associated systemic diseases, including cerebrovascular and cardiovascular diseases as well as hearing loss, cognitive dysfunction, pelvic organ prolapse, inguinal hernia, and chronic obstructive pulmonary disease (COPD).

“More research is needed to understand the biologic basis for these associations,” Dr. Ritch said. “One finding of particular interest is that hyperhomocysteinemia is present in more than two-thirds of patients with XFS and is a feature of many of the systemic diseases that are associated with XFS.”

Despite its systemic disease associations, XFS was not found to be associated with an increased risk for mortality according to several papers, he said.

“Interestingly, as well, although people with XFS are at increased risk for developing COPD, patients with both diseases live longer than those with COPD but not XFS,” Dr. Ritch concluded. ■

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**Small Drop Delivers Big Advancement**

**From His Perspective,** first as an ophthalmologist and as someone who has brought many innovative technologies into his field, Tsontcho Sean Ianchulev, MD, MPH, shares how he has come to realize how antiquated and inadequate is the existing paradigm of topical drug delivery.

There is virtually no other situation in medicine where physicians prescribe a therapeutic to patients knowing that, most of the time, they do not receive the correct dose. In the case of pills and injectable drugs, we know that if have prescribed 250 mg of Augmentin or 10 units of insulin, for example, and that is what the patient gets.

Go to OphthalmologyTimes.com/SmallDrop

**Glaucoma Experiences Transformative Growth**

**The Subspecialty of** glaucoma is experiencing a renaissance with promise in a greater number of therapies, exciting research, and the brightest talent being attracted to the profession, according to Kuldev Singh, MD, MPH.

Dr. Singh made an analogy to the European Renaissance—a period of intellectual enlightenment from the 14th century to the 17th century—to glaucoma’s current renaissance. Before the European Renaissance, the Middle Ages represented a bleak period in history when wars, famine, and the lack of progress by those with power hindered the advancement of the arts and sciences.

Go to OphthalmologyTimes.com/Growth

**No Strategies Exist to Lower Glaucoma Risk; Healthy Habits Offer Starting Point**

**Although There Are No** scientifically proven ways to prevent glaucoma, healthy habits—such as moderate exercise, regular visual check-ups, and eating green, leafy vegetables—represent a good starting point for a prevention strategy.

Louis R. Pasquale, MD, FARVO, professor of ophthalmology, Harvard Medical School, Boston, discussed environmental risk factors for glaucoma and pointed out there are no proven strategies to prevent the disease. He also offered some strategy suggestions.

Go to OphthalmologyTimes.com/Habits

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**Special Report**

**Pharmacologic Management of Glaucoma**

(Continued from page 13)

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**Robert Ritch, MD**

E: ritchmd@earthlink.net

This article was adapted from Dr. Ritch’s presentation during Glaucoma Subspeciality Day at the 2018 meeting of the American Academy of Ophthalmology. Dr. Ritch did not indicate any proprietary interest in the subject matter.
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Simple Drops Compounded Formulations**

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Therapeutic option improves outflow through trabecular meshwork
Exploring broad utility of netarsudil for ROCK inhibition across spectrum of glaucoma

By Gagan Sawhney, MD; Special to Ophthalmology Times

DESPITE significant progress in the fight against glaucoma, the human cost of this disease remains unacceptably high. According to the World Health Organization, it is the second-leading cause of blindness worldwide. Though we’ve managed to reduce the long-term probability of going blind in one eye from glaucoma from 25.8% to 13.5% in recent decades, a significant portion of patients still progress to blindness.1 As a glaucoma specialist who sees more than 60 patients/day, this is a terrifying statistic. Unfortunately, glaucoma is still a leading cause of blindness even under our care.

Why does glaucoma still present such a therapeutic challenge? First, it is underdiagnosed. We are missing early disease; once damage is done, it cannot be reversed.

Second, when we do diagnose and begin to treat glaucoma, too often we are not reaching target pressures, or not setting them low enough to begin with.

Third, when we do treat adequately, lack of compliance often impedes outcomes. The need to take multiple therapies several times a day, as well as the topical and systemic adverse events (AEs) associated with those therapies, affect patients’ ability to take medications as prescribed. Though a variety of promising surgical options have been introduced, these procedures do not come without potential AEs.

**MEDICAL THERAPY**

**LANDSCAPE**

For the past 20 years, we have relied on an armamentarium that includes prostaglandin analogs (PGAs), alpha-adrenergic receptor agonists (alpha-agonists), beta-adrenergic receptor antagonists (beta-blockers), and carbonic anhydrase inhibitors (CAIs).

These therapies generally promote aqueous outflow via the uveoscleral pathway or decrease aqueous production at the level of the ciliary body. What is astonishing is that even though the trabecular meshwork is primarily responsible for aqueous outflow and subsequently becomes dysfunctional in open-angle glaucoma, we have not had a therapy that primarily targets this pathway until now.

Approved by the FDA in December 2017, netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals) is the first in a class of glaucoma medications called Rho kinase (ROCK) inhibitors. ROCK activation inhibition is thought to prevent contraction of trabecular meshwork stress fibers and reduce resistance to aqueous humor outflow by disrupting actin-myosin contraction, decreasing extracellular matrix production and relaxing the tissue.

This glaucoma medication is the first to improve trabecular meshwork outflow through this unique mechanism of action (MOA).

Leading to the drug’s approval were three clinical trials—ROCKET 1, 2, and 4—which examined its safety and efficacy dosed q.d. compared with timolol b.i.d.

Pooled results demonstrated once-daily netarsudil to be non-inferior to twice-daily timolol in patients with baseline IOP below 25 mm Hg, producing a mean reduction of IOP at peak of up to 5 mm Hg. This effect was maintained through 12 months. Maximum efficacy results were achieved at week 1 with netarsudil, comparing favorably with PGAs, which typically take about 4 to 6 weeks to achieve maximal response.

Netarsudil consistently lowered IOP at the same level of mm of Hg regardless of the starting IOP, differing from timolol, which did not perform as well at lower IOPs but better at higher IOPs.

This is important because 80% of U.S. glaucoma patients have IOPs that are less than or equal to 26 mm Hg at time of diagnosis.5 Because netarsudil reduces both perfusion pressure and episcleral venous pressure (EVP), it can maintain more consistent efficacy across a larger range of IOPs.

The most commonly observed ocular AE in the ROCKET trials was conjunctival hyperemia (reported in 53% of patients), which appeared after two weeks of treatment and either resolved or did not progress with continued dosing.

Importantly, in the ROCKET trials, after a washout period and prior to starting treatment with netarsudil, there was a baseline hyperemia rate of 20% that was not factored out of this statistic. In 9 out of 10 patients, hyperemia was either not reported or reported as mild.

In my patient population, I am seeing a 30% hyperemia rate. Fortunately, the hyperemia is mild and mostly well tolerated.

Other ocular AEs (~20%) included cornea verticillata, instillation site pain, and conjunctival hemorrhage. Conjunctival (petechial) hemorrhage was graded as mild in more than 90% of cases. Cornea verticillata, likely a result of netarsudil-induced phospholipidosis, was mild and seen only under biomicroscopy, unlike cases often associated with amiodarone. Most cases resolved or improved by the end of a noninterventional follow-up study and were not associated with any clinically meaningful impact on visual function.

Netarsudil has no labeled systemic contraindications, and unlike beta-blockers and alpha-agonists, does not have any effect on blood pressure or heart rate.

**PHYSICIAN EXPERIENCE**

When I first heard about netarsudil, I was cautiously optimistic about the potential utility of a therapeutic option that improves outflow through the trabecular meshwork. I was also encouraged by the potential to enhance compliance given its once-daily dosing and mild AE profile.

To date, I have written more than 150 netarsudil prescriptions for patients across the entire glaucoma disease spectrum, including primary-open angle glaucoma (POAG) and normal/low-tension glaucoma (NTG/LTG). I began

take-home

Based on his experience and depending on the glaucoma patient, Gagan Sawhney, MD, explains why he considers netarsudil to be a valuable first- or second-line agent, as well as an effective addition to maximum medical therapy.

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- Netarsudil has no labeled systemic contraindications, and unlike beta-blockers and alpha-agonists, does not have any effect on blood pressure or heart rate.
prescribing netarsudil as a second- or third-line adjunctive agent in mild to moderate disease.

One of these patients, a 70-year-old female, presented with a history of mild POAG OD and moderate POAG OS with a Tmax of 30 mm Hg OD and 32 mm Hg OS that was progressing at current IOPs of 17 mm Hg OD and 16 mm Hg OS. The patient was on a PGA q.h.s. OU and C1 b.i.d. OU. Humphrey visual field mean deviation OD was –2.35 and mean deviation OS was –11.24. I added netarsudil q.h.s. OU to the patient’s regimen. At her four-week, follow-up appointment, IOPs were 10 mm Hg OD and 11 mm Hg OS, thus achieving goal pressures.

**CASES WITH MORE SEVERE DISEASE**

I have also had success with netarsudil in patients with more severe disease. One severe POAG patient was referred to me after having undergone a failed trabeculectomy and subsequent bleb needling. The patient was on three agents and had an IOP of 36 mm Hg. I recommended tube shunt surgery, but the patient was unwilling to undergo an additional procedure.

As a compromise, I prescribed netarsudil, which brought the IOP to 17 mm Hg, allowing us to avoid surgery. While this response is not typical (as evidenced by the trials in which a mean IOP reduction of up to 5 mm Hg was observed), this patient is an example of a small number of those I consider “hyper-responders” to netarsudil where IOP reduction is greater than what is demonstrated by the ROCKET studies.

I have also had positive experience with netarsudil in NTG. The Collaborative Normal Tension Glaucoma Study Group recommended a 30% reduction in IOP for NTG to effectively slow the progression of glaucoma. I am now using netarsudil as a second- or third-line agent in the setting of NTG. I consider netarsudil a valuable first- or second-line agent, as well as an effective addition to maximum medical therapy. I believe netarsudil can be used across the entire spectrum of glaucoma, from mild to severe disease in patients who are taking 0–1 drops to maximum medical therapy.

**SUMMARY**

Netarsudil addresses some of the most important issues associated with IOP-lowering therapies. Its MOA offers consistent IOP lowering regardless of baseline pressure or number of currently prescribed drops, and its q.d. dosing helps with compliance. It has a favorable safety profile, with minimal systemic AEs, no contraindications, and a generally tolerable ocular safety profile (in clinical studies, 53% of patients reported conjunctival hyperemia).

Discussing potential side effects, such as hyperemia, with patients in advance of prescribing can help allay undue concerns and allow ample time to make an informed decision about continuation of therapy together based on efficacy and tolerability.

Coverage for this medication is expanding rapidly but obtaining a prior authorization will help avoid frustration for patients and office staff.

Based on my experience and depending on the patient, I consider netarsudil a valuable first- or second-line agent, as well as an effective addition to maximum medical therapy. I believe netarsudil can be used across the entire spectrum of glaucoma, from mild to severe disease in patients who are taking 0–1 drops to maximum medical therapy.

**References**


Which MIGS for which patient?

Here is one question to help clinicians decide: ‘What is the anatomy giving me?’

By Conni Bergmann Koury; Reviewed by Brian A. Francis, MD, MS

TO CHOOSE the right micro-invasive glaucoma surgery (MIGS) procedure, glaucoma specialists must consider several questions, according to Brian A. Francis, MD, MS. Among these questions:

- Is there a coexistent cataract?
- What is the diagnosis?
- What is the anatomy?
- What is the target IOP?
- What medications can the patient use?
- What is the patient’s preference and lifestyle?

Glaucoma surgeries can be categorized based on one of four mechanisms of action, according to Dr. Francis, professor of ophthalmology and holder of the Stieger Endowed Chair at the Doheny Eye Institute and Stein Eye Institute, David Geffen School of Medicine, University of California, Los Angeles (UCLA).

These categories include the trabecular outflow, suprachoroidal outflow, aqueous humor production, and subconjunctival outflow.

**TRABECULAR OUTFLOW**

Regarding procedures that target trabecular outflow, surgeons can choose Schlemm’s canal dilation—which can be done with or without cataract extraction (CE)—or Schlemm’s canal unroofing procedures. The technique can be performed with or without cataract extraction, and it can treat a greater amount of the angle.

For 180° of trabecular removal, surgeons can consider the Trabeculectomy or Goniotome (NeoMedix) or the Kahook Dual Blade (New World Medical).

Gonioscopy-assisted transluminal trabeculotomy can be used to treat 360°, as can the Trab360 (Sight Sciences) and Omni procedures.

**SUPRACHOROIDAL OUTFLOW**

Procedures that target suprachoroidal outflow are combined with CE. They make use of the suprachoroidal space and uveoscleral outflow. The withdrawn Cypass (Alcon Laboratories) is one such device.

Methods of Schlemm’s canal dilation—which can be done with or without cataract extraction (CE)—include ab interno canaloplasty, a 360° treatment, and viscodilation of Schlemm’s canal with a catheter. This can be accomplished with Visco360 and the Omni procedures (Sight Sciences).

The iStents (generation 1 and 2; Glaukos) and the Hydrus Microstent (Ivantis) are implants that target trabecular outflow.

This mechanism can also be approached via Schlemm’s canal unroofing procedures. The technique can be performed with or without cataract extraction, and it can treat a greater amount of the angle.

For 180° of trabecular removal, surgeons can consider the Trabectome or Goniotome (NeoMedix) or the Kahook Dual Blade (New World Medical).

Gonioscopy-assisted transluminal trabeculotomy can be used to treat 360°, as can the Trab360 (Sight Sciences) and Omni procedures.

**SUBCONJUNCTIVAL OUTFLOW**

“Surgeons should have at least two MIGS procedures in their tool kit that use different mechanisms of action and should always consider what the goal is, what the eye is giving you, and what the patient wants.”

— Brian A. Francis, MD, MS
do produce a bleb and we use mitomycin,” Dr. Francis said. These are designed to lower IOP similar to traditional filtration such as trabeculectomy or aqueous tube shunt, but with lower complication rates. These include the ab interno approach (XEN Gel Stent, Allergan) and the ab externo approach with the investigational glaucoma drainage system (InnFocus MicroShunt, Santen; not yet FDA approved).

**BACK TO THE KEY QUESTIONS**

**IS THERE A CATARACT?**
The MIGS procedures that are FDA approved in conjunction with cataract extraction are the iStent, iStent inject, and the Hydrus.

“In patients on multiple medications, we should consider MIGS along with cataract extraction even if the patient is well controlled to reduce the medication burden,” according to Dr. Francis.

Trabecular MIGS without a device is an option independent of cataract status.

Angle-closure glaucoma may improve with cataract extraction alone, he noted.

Because ECP is difficult in a phakic eye, it must be performed with cataract surgery or in pseudophakes, Dr. Francis noted.

**DIAGNOSIS AND ANATOMY**
In primary and secondary open-angle glaucomas, all procedures are on the table, Dr. Francis said.

The same is true of pigmentary glaucoma. In a narrow angle, glaucoma intervention should be combined with cataract extraction if possible, and caution should be exercised with implants.

“In chronic-angle closure, you can consider MIGS plus goniosynechialysis or aqueous inflow or subconjunctival procedures,” Dr. Francis noted.

**TARGET IOP**
In Dr. Francis’ experience, angle procedures result in IOPs in the 14 to 17 mm Hg range, suprachoroidal, a 13 to 15 mm Hg range, aqueous inflow procedures can achieve a 30% reduction, and subconjunctival filtration results in pressures 10 to 14 mm Hg.

“Do not forget that procedures can be combined for greater efficacy in patients with more advanced disease in need for lower target IOPs,” he said. “Patients intolerant to medications also require more aggressive treatments.”

**CONCLUSION**
Dr. Francis said he believes that glaucoma surgeons should have at least two or more procedures with different mechanisms of action in their tool kit—techniques that have options for phakic and pseudophakic patients, said Brian A. Francis, MD, MS.

He said that surgeons should think about combining procedures and always know what they want to accomplish for each patient, based on what the eye is “giving you” and what the patient wants.

‘Do not forget that procedures can be combined for greater efficacy in patients with more advanced disease in need for lower target IOPs.’ — Brian A. Francis, MD, MS

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**Special Report**

**PHARMACOLOGIC MANAGEMENT OF GLAUCOMA**

**BRIAN A. FRANCIS, MD, MS**

E: bfrancis@doheny.org

This article was adapted from Dr. Francis’ presentation during Glaucoma Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology. He is a speaker for Alcon Laboratories, Allergan, Diopsys, and Innfocus, and is a consultant to Allergan, Bausch + Lomb, Diopex, Endo Optiks, Glaukos, and NeoMedix.

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Sustained-release delivery systems on horizon of glaucoma care

Novel platforms address adherence; clinicians look to efficacy, treatment duration

By Lynda Charters; Reviewed by James D. Brandt, MD

COMPLIANCE is a huge issue in patients with glaucoma despite the effectiveness of the available anti-glaucoma drugs. However, while no one can argue with the safety and efficacy of the prostaglandin analogues—the first-line treatments for glaucoma—many patients do not, cannot, or will not instill their medications, said James D. Brandt, MD. In fact, 50% of glaucoma patients are guilty of noncompliance.

Sustained-release platforms will help address this problem. Many such systems are under development, and a few may be commercially available within the next few years, said Dr. Brandt, professor of ophthalmology and vision science, vice chairman for International Programs and New Technology, and director of the glaucoma service, Tschannen Eye Institute, University of California, Davis.

Developing sustained-release platforms is challenging. The primary concerns of efficacy and treatment duration are critical, but they must be balanced with patient comfort, experience, and safety.

“It is my firmly held belief that in early glaucoma and ocular hypertension, safety must take the front seat among all the considerations,” Dr. Brandt said. “In the Ocular Hypertension Treatment Study, we found that we had to treat 20 patients to prevent early disease from developing in one patient.”

This raises the flip side of the question, i.e., What number is needed to harm? What are the risks of infection? How does the cornea tolerate? How is the endothelial cell count affected? What are the risks of infection?

For patients with advanced disease, the risk-to-benefit ratio can change if better efficacy and treatment duration can be achieved.

DEVELOPMENT PIPELINE

A number of approaches can be used to provide sustained-release drugs: some are implantable under the conjunctiva, e.g., erodible drug pellets, drug-containing microspheres, and mechanical drug reservoirs, and some are used externally, such as drug-infused contact lenses placed on the cornea.

Consideration is also being given to intracamerally, punctal, and conjunctival designs, which are among the farthest in the pipeline. An intracameral erodible device, a drug-eluting punctal plug, and a drug-eluting conjunctival ring are either in or near phase III trials and likely to be marketed within a few years, he noted.

As of late 2018, products thought to be available within 3 to 5 years include two anterior chamber biodegradable implants (Bimatoprost SR, Allergan and Travoprost XR-ENV 515, Envisia Therapeutics); a nondegradable anterior chamber implant (iDose, Glaukos); a conjunctival pericocular ring (bimatoprost ring, Allergan); and two punctal plugs (OTX-TP, Ocular Therapeutics and Evolute, Mati Therapeutics).

The device closest to commercial availability is the Bimatoprost SR device, currently in a phase III study. The device, which can be injected in the office, continuously releases the drug for a minimum of 6 months. Data obtained in the phase II study of the device showed sustained IOP lowering out to 6 months.

Phase III trials will likely begin soon for a few devices. iDose, a titanium implant, contains at least a 6-month supply of travoprost. The device is placed and can be replaced over time in the trabecular meshwork. Preliminary data currently are unpublished.

The Travoprost XR is an intracameral erodible platform; early phase II data indicate that IOP lowering continued out to 11 months in five patients. The two punctal plugs, OTX-TP and Evolute, are in phase III and II trials, respectively; both deliver prostaglandins and have a targeted treatment duration of 90 days, he noted.

Dr. Brandt has been working with the bimatoprost ring, for which phase II studies have been completed and phase III studies are planned. The device is implanted into the conjunctival fornix and rests under the eyelids. The device must be replaced by a surgeon every 3 to 6 months. Rings containing more than one drug have been evaluated in small pilot studies.

REALITY CHECK

The future of glaucoma therapy seems bright, but is not without as-yet unanswered questions. Clinicians should consider the predictability of the treatment duration.

“Until these products have been used for a while, we won’t know how the duration varies among patients,” Dr. Brandt said.

In the absence of knowledge of the real-world duration, patients whose IOPs have increased weeks or months before the label duration can be missed, he said.

When considering any sustained-release platform, it is noteworthy that IOP increases are asymptomatic. Home tonometry is useful in this scenario.

A second consideration is the need to remove the platform if patients experience drug side effects and the consequences of development of cystoid macular edema after a prostaglandin depot is implanted.

About 50% of patients cannot control their glaucoma with only one drug and need two or more to decrease IOP by 20%. He emphasized the importance of not overpromising to patients that they will have a drop-free life.

Sustained-release platforms that are injected are associated with specific questions regarding workflow and safety. For example, because glaucoma usually occurs bilaterally, should both eyes be injected on the same day? And how is the need for more than one drug addressed?

In addition, how many injections can the cornea tolerate? How is the endothelial cell count affected? What are the risks of infection?

The phase III trials cannot answer these questions, only time will provide answers, Dr. Brandt concluded.
I didn’t realize STARS were little dots that twinkled

—Misty L, RPE65 gene therapy recipient

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LATANOPROSTENONE bunod ophthalmic solution 0.024% (LBN) (Vyzulta, Bausch + Lomb) is a safe and effective addition to the IOP-lowering treatment armamentarium, and seems to offer particular value for managing patients who do not respond adequately to traditional first-line therapy, including those with a lower initial IOP, said Andrew G. Iwach, MD.

“The introduction of latanoprost more than two decades ago dramatically changed management for patients with elevated IOP and because of its effectiveness, greatly helped reduce the need for glaucoma surgery,” said Dr. Iwach, executive director, Glaucoma Center of San Francisco, and co-founder, Eye Surgery Center of San Francisco, San Francisco.

“Compared with latanoprost, LBN provides a potential additional mechanism of action for IOP-lowering that explains why it may be even more effective and have a particular benefit in certain patients,” Dr. Iwach said.

Latanoprostene bunod is a nitric oxide (NO)-donating prostaglandin FP receptor agonist that is metabolized in the eye into two moieties—the F2a prostaglandin analog, latanoprost acid, and butanediol mononitrite from which NO is released. Latanoprost acid lowers IOP by increasing aqueous humor outflow through the uveoscleral pathway whereas NO introduces a second mechanism, increasing aqueous humor outflow through the trabecular meshwork and Schlemm’s canal.

Trial results evaluating LBN are consistent with the idea that its potential dual mechanism of action confers LBN with enhanced IOP-lowering activity.

Pivotal trials evaluating once-daily treatment with LBN 0.024% [LUNAR (Medeiros FA, et al. Am J Ophthalmol. 2016;168:250-259) and APOLLO (Weinreb RN, et al. Ophthalmology. 2016;123:965-973)] showed that it was significantly more effective than timolol 0.5% administered twice daily.

In the phase II VOYAGER study, LBN 0.024% was associated with a significantly greater reduction in diurnal IOP compared with latanoprost 0.005% [Weinreb RN, et al. Br J Ophthalmol. 2015;99:738-745].

Results of the open-label noncomparative JUPITER study [Kawase K, et al. Adv Ther. 2016;33:1612-1627] suggest LBN may have a niche role for treating patients with lower starting IOP. In JUPITER, which was conducted in Japan and predominantly enrolled patients with a baseline IOP ≤21 mm Hg, the IOP reduction achieved with LBN 0.024% was similar to that reported for latanoprost 0.005% in a Japanese cohort with a baseline IOP ≤21 mm Hg.

“Most ocular hypotensive medications drugs are more effective the higher the initial IOP,” Dr. Iwach said.

In the VOYAGER study, the average reduction from baseline IOP was about 1 mm Hg greater with LBN compared with latanoprost, which may not seem that important. However, there was a lot of variability in the response to LBN with some patients achieving an IOP reduction that was 3 to 4 mm Hg greater than the latanoprost mean.

In my experience, the switch from latanoprost to LBN has also been very smooth in terms of tolerability,” he said. “All of the medications we use have potential side effects, but the safety profile of LBN seems similar to that of latanoprost, and changing treatment to LBN has not resulted in a significant increase in patient complaints.”

Dr. Iwach is a consultant to and on the speakers’ bureau for Bausch + Lomb.

By Cheryl Guttman Krader; Reviewed by Andrew G. Iwach, MD

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**Special Report**

**PHARMACOLOGIC MANAGEMENT OF GLAUCOMA**

**Novel IOP-lowering medication finds utility in glaucoma patient care**

Latanoprostene bunod especially useful to patients who do not respond to first-line therapy

By Cheryl Guttman Krader; Reviewed by Andrew G. Iwach, MD
Drug availability, pricing negatively affect the practice of glaucoma

Steps to drive costs down include patient education, greater competition in marketplace

By Vanessa Caceres

Physicians, insurers, pharmacists, regulators, and patients should all be part of the mix in making glaucoma medications more affordable, said Joshua D. Stein, MD.

This can be challenging, and prices for many glaucoma medications continue to increase, said Dr. Stein, University of Michigan, Ann Arbor, MI.

The main reasons for high medication prices in the United States are market exclusivity and limited competition. New agents typically are awarded 7 years of market exclusivity by the FDA.

However, the actual median length of market exclusivity is 12 years for most medications and more than 14 years for first-in-class medications.

This is because that time period of exclusivity can extend due to regulatory review, clinical trials, or testing done in children, Dr. Stein said.

“For glaucoma medications, the time of patent exclusivity ranges from 7 to 15 years for common agents,” Dr. Stein said.

Drug shortages also can affect patient use of drugs. Some contributing factors for this include a lack of raw ingredients, which was the reason cited for a limited supply of dorzolamide and dorzolamide-timolol, Dr. Stein explained.

Dorzolamide-timolol and latanoprost are two examples. Dr. Stein explained. “Physicians aren’t necessarily aware of the price differential between different medications,” Dr. Stein said.

“Pharmacists filling prescriptions aren’t encouraged to do medication substitutions,” he added. “Patients with good insurance are often insulated from the price of the medication they are receiving, and all of this leads to higher-priced medications.”

Other factors that affect drug prices include when companies slightly change the formulation of a branded product, which in turn can limit or delay the entry of competitors; a lack of raw ingredients, company mergers, and a lack of negotiating power at a national level on behalf of programs like Medicare.

All of these barriers have led to physicians spending a good deal of time nowadays managing prior authorizations, Dr. Stein said.

“So some say there is more time spent on that than with patients, which is really sad,” he said.

When prices for drugs remain high, patient care is affected, explained Dr. Stein, citing a study he led that compared generic latanoprost with branded latanoprost, which found that patients who continued to use branded latanoprost were 28% less likely to have improved adherence and 39% were more likely to have reduced adherence.1

Other factors include a limited number of companies producing medications (such as pilocarpine and atropine), a lack of supply for medications available for sale, and a lack of viable alternatives. Even when there is more than one branded version of a product available, prices can still be high.

“Physicians aren’t necessarily aware of the price differential between different medications,” Dr. Stein said.

“Pharmacists filling prescriptions aren’t encouraged to do medication substitutions,” he added. “Patients with good insurance are often insulated from the price of the medication they are receiving, and all of this leads to higher-priced medications.”

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Patient education matters

Dr. Stein described a card given to some glaucoma fellows on rotation that shows the different prices of glaucoma medications in a given class, all with prices taken from GoodRx.com. The card helps to educate trainees and clinicians about price differences.

The use of microinvasive glaucoma surgery or other surgical approaches is another option when drugs are not affordable, Dr. Stein added. Dr. Stein concluded by noting that American Glaucoma Society leaders are working on the topic of drug cost by educating the FDA and insurers.

Reference


Steps to help lower prices

Despite the discouraging news about drug costs, Joshua D. Stein, MD, said there are ways to help lower prices. Here are his recommendations:

- Encourage greater competition among drug products.
- Crack down on companies that are trying to prevent the entry of generic products.
- Reduce pharmaceutical companies’ research and development costs.
- Limit expensive direct-to-consumer drug advertising.
- Make it easier for generic medications to enter the marketplace.
- Create laws to make it easier for pharmacists to substitute branded drugs for less costly generics.
- Pass laws in Congress that make it easier to import drugs from outside the United States.
- Allow the Centers for Medicare and Medicaid Services to negotiate prices for Part D drug plans.
- Perform more cost-effectiveness analyses comparing medications.
- Educate physicians and patients about comparative drug costs.

JOSHUA D. STEIN, MD

jdstein@med.umich.edu

This article was adapted from Dr. Stein’s presentation at the 2018 meeting of the American Academy of Ophthalmology. Dr. Stein has no related disclosures.
**The History** of glaucoma medications is punctuated by once-promising drugs since abandoned because of significant side effects or superseded by newer, more effective products as well as a few that have—so far—retained a place in the armamentarium alongside newer agents.

“We’ve come a long way, and new things are on the horizon,” said Wallace L.M. Alward, MD, Frederick C. Blodi Chair, Department of Ophthalmology, University of Iowa Carver College of Medicine, Iowa City.

Eserine (physostigmine) was the first glaucoma drug, a cholinergic agonist dating from 1876. Derived from the West African calabar bean, which caused pupils to become smaller, it was initially used for miosis in iridectomy cases, then found to lower IOP and break angle-closure attacks.

Pilocarpine was introduced just a year later, but while it wasn’t until 1946 that the first indirect-acting cholinergic agonist, diisopropyl fluorophosphate, was discovered, followed by echothiophate iodide (Phospholine iodide) in 1957.

Gel and extended-release formulations of pilocarpine were introduced as a means of decreasing the need for frequent dosing as well as reducing side effects—one physician described instilling eserine 40 to 50 times a day—and these remained the only successful long-term medical options for glaucoma until acetazolamide came onto the scene in 1954.

In the interim, the search for better glaucoma medication traveled down pathways such as crystalline alkaldoids, including the rat poison strychnine, administered hypodermically in large doses to relieve the “mental and physical depression” of glaucoma, a contemporary physician reported in the 1890s.

Osmotic agents were added to the list of available agents in the early 1900s, starting with hyperosmotic saline in 1904, joined by glucosce, urea, mannitol, and glycero.

Next to find a place on the roster were the adrenergic antagonists, reaching the market in the late 1940s. Patients given intravenous dibenamine often experienced IOP levels dropping below 25 mm Hg for up to 24 hours. Unfortunately, it was only effective if administered intravenously, Dr. Alward said, and had significant side effects such as severe orthostatic hypotension. Long periods of bed rest were recommended, and some deaths were reported. Carbonic anhydrase inhibitors were introduced in 1954. Though still used today, these drugs are known for a host of side effects, he said.

In 1955, adrenergic agonists followed the adrenergic antagonists onto the market. Topical epinephrine lowered IOP but led to both topical and systemic side effects. In one study, 80% of patients had to discontinue therapy. The IOP-lowering effects of beta-adrenergic antagonists were discovered in 1967, but problems such as decreased tear production, corneal anesthesia, and tachyphylaxis stalled commercial use until timolol was found to be both effective and well tolerated a decade later. Following rapid FDA approval, Timoptic became available in 1978.

**Flash Forward to the 1980s**

The alpha-adrenergic agonists were the next new class of glaucoma medication, introduced around 1987. Apraclonidine, a derivative of clonidine, was initially used with laser iridotomies to control bleeding.

“That didn’t actually work, but serendipitously it was found it prevented IOP spikes,” he said. Apraclonidine (Iopidine, Alcon Laboratories) was initially approved for post-laser IOP rise in 1993 for chronic glaucoma management as well. Brimonidine (Alphagan, Allergan), reaching the market in 1996, largely replaced apraclonidine.

The 1990s also saw the culmination of decades of research into making a topical carbonic anhydrase inhibitor that would reduce the side effects of the oral version. Dorzolamide (Trusopt, Merck), released in 1995, is still widely used.

Another new approach in the 1990s was the adrenergic agonist dipivefrin (Propine, Allergan), a prodrug converted to epinephrine as it passed through the cornea. It was hoped that it would reduce systemic side effects such as tachycardia and hypertension, and while this proved to be the case, dipivefrin, like other adrenergic drugs, it led to adverse effects such as topical allergies and is no longer available in the United States.

A much more successful class of glaucoma medication, also introduced in the mid-1990s, was the prostaglandin analogs. Discovered during research on the inflammatory cascade, their effectiveness at lowering IOP was demonstrated in animal models in 1982. However, it was another 14 years before latanoprost (Xalatan, Pfizer) reached the milestone of being the first prostaglandin analog to receive FDA approval. Physicians quickly turned to Xalatan and other prostaglandins as their go-to medications due to their efficacy, safety, and daily dosing.

Preservative-free versions and prostaglandin-combination drugs have subsequently been approved, and the most recent advance was the 2017 approval of a nitric oxide-donating prostaglandin analog, latanoprostene bunod (Vyzulta, Bausch + Lomb).

The arrival of a new class of glaucoma drugs, the first major innovation in glaucoma therapy since the 1996 approval of prostaglandins, was signaled by the 2017 approval of a nitric oxide-donating prostaglandin analog, latanoprostene bunod (Vyzulta, Bausch + Lomb), a Rho kinase inhibitor.

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### Take-home

- The quest for safe and effective glaucoma medications is one of setbacks and successes, accidental discoveries, and decades of targeted research, as well as an ongoing effort.

### Timeline

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<tr>
<th>YEAR</th>
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<td>1877</td>
<td>Cholinergic agonists</td>
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<td>1897</td>
<td>Crystalline alkaloids</td>
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<td>1904</td>
<td>Osmotic agents</td>
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<td>Adrenergic antagonists</td>
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<td>2017</td>
<td>Rho kinase inhibitors</td>
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Prescribing corticosteroids plus nonsteroidal anti-inflammatory drugs is routine for the management of inflammation and pain after cataract surgery. Prolonged inflammation puts patients at increased risk of secondary ocular complications that include IOP spikes, cystoid macular edema, posterior synechiae formation, and posterior capsule opacification. Patients with untreated postoperative pain are likely to be less happy with their surgery.1–3

Despite common use, the dosing frequency of postoperative cataract surgery medications—topical drops—is suboptimal.

Drops are problematic for several reasons, including poor adherence by patients, ineffective formulations, and inconsistent bioavailability. Numerous studies show that patients not only have difficulty successfully administering the correct number of drops, but they often miss their eye altogether.4–7

Consider the following as aspects of the clinical reality of patients and eye drops: the burden of regimen frequency and complexity, forgetfulness, and issues with physical dexterity (particularly in the elderly). This combination of factors has a negative impact on the efficacy of postoperative topical medications.8,9

SUSTAINED-RELEASE ALTERNATIVE

A sustained-release dexamethasone ophthalmic insert for intracanalicular use (Dextenza, Ocular Therapeutix) (0.4 mg dexamethasone) may be an alternative. The surgeon postoperatively places the hydrogel insert containing dexamethasone in the canaliculus, where it then provides a sustained and tapered delivery of the drug to the ocular surface over the next 30 days.

Sustained release of dexamethasone reduces the risks of improper corticosteroid tapering and unwanted fluctuations in drug concentration.10 It also avoids the peaks and valleys associated with topical drop administration.

A preclinical model showed that the insert has the potential to increase bioavailability (versus topical drug use) from 5% to 70%,11 and the amount of drug used is just a small portion of the total dose a patient would take during a typical monthly topical course.

The burden of patient adherence is eliminated, and the side effects associated with the topical administration of corticosteroids may be reduced with this delivery mode. The dexamethasone formulation is preservative-free, and the hydrogel insert softens over time and is cleared through the inferior nasolacrimal canaliculus.

If necessary, the insert can be expressed.

The dexamethasone insert’s efficacy was evaluated in patients for pain and inflammation in patients undergoing cataract surgery was shown in two multicenter, randomized, phase III registration trials (n = 488).

A statistically significantly greater proportion of subjects receiving the insert in both studies were found to have an absence of pain at day 8 compared with those receiving placebo (study 1: 80.4% versus 43.4%, p < 0.0001, difference: 37.0%; study 2: 77.5% versus 58.8%, p = 0.0025%, difference: 18.7%).

A greater proportion of subjects in the dexamethasone group had an absence of anterior

TAKE-HOME

› A dexamethasone ophthalmic insert for intracanalicular use may be a sustained-release alternative to the dosing frequency of postoperative cataract surgery topical drop therapy.
AC CELL SCORE

(Continued from page 25)

chamber (AC) cells at day 14 in both studies as well. This difference was statistically significant in the first but not the second study.\textsuperscript{12}

The dexamethasone insert’s safety profile was favorable in both studies, and the most common adverse events were AC inflammation (insert 5.9% versus placebo 7.3%), increased IOP (insert 5.6% versus placebo 4.3%), iritis (insert, 4.0%; placebo, 9.1%), and corneal edema (insert, 1.6%; placebo, 5.5%).\textsuperscript{12}

THIRD STUDY

A third phase IIIb study (published in the Journal of Cataract and Refractive Surgery) in patients undergoing cataract surgery was designed to further evaluate the efficacy of the dexamethasone insert on inflammation and pain.\textsuperscript{13,14} It was similar in design to the previous studies with some differences with respect to randomization, study visit schedule, and the use of rescue medication.

A total of 435 subjects completed the study (214 in the dexamethasone insert arm and 221 in the placebo insert arm). The demographics and baseline characteristics of the two groups were comparable, and the study met both of its primary endpoints.

At day 14, significantly more subjects in the dexamethasone insert arm compared with the placebo insert arm had an absence of anterior chamber cells at day 14 (52.3% versus 31.1%; \textit{p} < 0.0001). Also, at day 8, significantly more subjects in the dexamethasone insert arm compared with the placebo arm had an absence of ocular pain (79.6% versus 61.3%; \textit{p} < 0.0001).

INFLAMMATION: CLOSER LOOK

In terms of inflammation, at each time point between days 4 and 45, significantly more subjects assigned to the dexamethasone insert had an absence of AC cells compared with the placebo arm (\textit{p} < 0.05).

The mean AC cell score in the dexamethasone insert arm was lower than in the placebo arm at all postoperative study visits. Mean AC cell score (scale, 0–4) peaked in both treatment and placebo arms at day 1 postoperatively (study day 2), with the scores declining rapidly in the treatment arm (mean score, 0.44 by day 14) versus a slow decline in the placebo arm (mean score, 0.92 by day 14).

At all postoperative visits, fewer eyes assigned to the insert versus placebo arm had an AC cell score of grade \textasciitilde{3}, the level at which investigators could consider prescribing rescue medication. At each time point between day 2 and day 30, significantly more insert-assigned subjects compared with placebo (\textit{p} < 0.05) had an absence of AC flare.

Additionally, a significantly greater proportion of eyes in the dexamethasone arm were observed to have 5 or fewer AC cells at the day 14 visit versus placebo (81.5% versus 52.3%; \textit{p} < 0.0001). The mean AC flare score in the insert-assigned subjects peaked at the day 2 visit (score, 0.8), declining steadily and reaching 0.1 by the day 30 visit.

The mean AC flare score in the placebo arm was highest at the visits on days 2, 4, and 8 (score, 0.9), declining to 0.2 by day 45. Few eyes experienced a flare score of grade \textasciitilde{3}, the level at which investigators could consider prescribing rescue medication.

PAIN: DEEPER DIVE

At each time point between days 2 and 30, significantly more subjects in the dexamethasone insert arm had an absence of ocular pain arm compared with placebo (\textit{p} < 0.05). Eyes in the insert arm had a peak mean ocular pain score of 0.6 score units (scale, 0–10) at the day-2 visit and subsequently declined to a mean of 0.2 units at the day-45 visit.

The mean pain score in placebo group, on the other hand, was 1.2 units on day 2 and declined to 0.5 units by day 45. At the day 2 visit, 5.6% of subjects receiving the insert versus 11.3% of subjects receiving placebo reported moderate to severe ocular pain. If pain reached grade \textasciitilde{4}, then investigators could consider prescribing rescue medication. At day 8, 4.3% of subjects in the insert group reported moderate to severe pain versus 10.4% of subjects receiving placebo.

Fewer than 5% of subjects in both arms used rescue medication through day 8. At day 14, 5.6% of subjects in the dexamethasone insert arm, compared with 10.9% of subjects in the placebo arm used rescue medication.

SAFETY

A total of 29.2% of subjects in the dexamethasone insert arm and 38.9% in the placebo arm experienced at least one adverse event (AE). One AE in the dexamethasone insert arm, increased lacrimation in the study eye, was judged to be related to treatment. AEs were primarily ocular in nature, with 25.5% of subjects in the dexamethasone insert arm and 33.9% in the placebo group having at least one ocular AE in the study eye. The majority experienced events that were of mild or moderate severity; only three subjects in each treatment arm experienced an AE that was considered severe.

One serious AE in the dexamethasone insert arm was ocular in nature, a retinal detachment, it was not related to treatment.

The most common ocular AEs reported in the insert eye were inflammation (8.3%), increased IOP (7.4%), and AC inflammation (6/216; 2.8%). No treatment-related non-ocular AEs occurred, and no subjects were withdrawn from the study participation due to AEs.

CONCLUSION

An integrated assessment of efficacy across all three phase III Dextenza trials to date achieved statistical significance in both primary efficacy endpoints, with 42.7% of patients observed to have no AC inflammation cells at day 14 (placebo: 56.9%; \textit{p} < 0.0001), and 79.2% of patients observed to have no ocular pain at day 8 (placebo: 27.5%; \textit{p} < 0.0001).\textsuperscript{14}

The sustained-release intracanalicular dexamethasone insert’s design allows for a constant, low-dose drug load to the ocular surface with no preservatives, better bioavailability, and a self-tapering of corticosteroid delivery postoperatively.

Additionally, the insert is absorbable and can be removed, if necessary.

Most importantly, the surgeon-placed insert removes a significant part of the treatment burden of a complex postoperative regimen of topical eye drops.

By 2020, 30 million Americans may have cataracts, based on U.S. census data and population-based studies.\textsuperscript{15} Optimizing the delivery of postoperative medications used to treat inflammation and pain would improve patients’ outcomes and overall surgical experience in a clinically meaningful way.
LADDER

(Continued from page 1)

for identifying disease activity. Patients in the ranibizumab group received monthly intravitreal injections.

Time until the first need for implant refill was analyzed as the primary end point. The results showed a clear dose response, with the interval being longest in the PDS 100 mg/mL group. Median time to first refill was 15 months in the PDS 100 mg/mL group, 13.0 months for the 40 mg/mL group, and 8.7 months in the PDS 10 mg/mL group.

Among patients in the PDS 100 mg/mL group, 93% had not yet met refill criteria at 3 months, 80% still did not need a refill at 6 months, and 69% went at least 9 months without a refill.

Functional and anatomic outcomes for patients receiving the PDS 100 mg/mL implant were comparable to those in the monthly ranibizumab group. Overall, the implant insertion surgery and refill procedures were well tolerated, and there were no meaningful differences between treatment arms in systemic safety, Dr. Regillo said.

"The techniques for device implantation and refilling are unique, but with training and meticulous care, they can be readily and safely adopted by vitreoretinal surgeons," Dr. Regillo said.

"The techniques for device implantation and refilling are unique, but with training and meticulous care, they can be readily and safely adopted by vitreoretinal surgeons." — Carl D. Regillo, MD

LADDER DESIGN
Patients were eligible for LADDER if they had been newly diagnosed with nAMD within the previous 9 months, received at least two prior anti-VEGF injections with the last one being ranibizumab at least 7 days prior to the screening visit, demonstrated response to prior anti-VEGF treatment, and had Snellen equivalent best-corrected visual acuity (BCVA) of 20/20 to 20/200.

The four treatment arms were well-balanced in their baseline demographic and ocular characteristics. Across the groups, mean BCVA was about 20/40, mean time from nAMD onset was 3 to 4 months, and mean number of prior anti-VEGF treatments was 2.7 to 3.1.

In the PDS arms, the criteria used to determine need for device refilling were: increase in central foveal thickness ≥75 μm compared with the average of the last two visits or ≥100 μm compared with the lowest on-study measurement; decrease in BCVA ≥5 ETDRS letters compared with the average of the last 2 visits or ≥10 ETDRS letters compared with the best on-study measurement; or new macular hemorrhage.

The primary end point analysis was done after the last entered patient reached the 9-month visit, which occurred when the median time on-study was 16.8 months.

"As expected, the treatment burden in the ranibizumab arm at the primary end point was 16.8 injections, but it was only 2.4 for the PDS 100 mg/mL group," Dr. Regillo said.

Across the PDS treatment arms, the BCVA outcomes were also best in the highest dose group. Beginning at the month 2 visit, BCVA gains were virtually identical at each monthly follow-up in the PDS 100 mg/mL and monthly ranibizumab 0.5 mg treatment groups.

At month 9, mean change from baseline BCVA was 5 letters in the PDS 100 mg/mL group and 3.9 letters in the monthly ranibizumab group. The visual gains were maintained in the high-dose PDS group through follow-up that was available to month 18.

"Data on central foveal thickness showed good exudative control that was also maintained throughout follow-up and favored the high-dose PDS arm," Dr. Regillo said.

SAFETY

Vitreous hemorrhage developed in 50% of the first 22 patients who had the PDS implanted. Enrollment was stopped, and the surgical procedure modified to include photocoagulation of the uvea before entry into the vitreous cavity. Among patients who had the device placed using the new technique, the rate of vitreous hemorrhage dropped to below 5%.

Rates of conjunctival erosion, retinal detachment, and infection were 1% to 2%. The incidence of cataract was 7.6% of eyes receiving the PDS and 7.3% in the intravitreal ranibizumab group.

SURGICAL STEPS

The implant is placed in the superotemporal quadrant of the pars plana about 4 mm posterior to the limbus in a one-time outpatient surgical procedure done in an operating room under local anesthesia with sedation.

TAKE-HOME

- Patients with neovascular age-related macular degeneration treated with ranibizumab 100 mg/mL delivered via the port delivery system in a phase II study went a median of 15 months before needing device refill. A phase III study is under way.

16.8 VS 2.4 INJECTIONS

The treatment burden in the ranibizumab arm at the primary end point was 16.8 injections, but it was only 2.4 for the PDS 100 mg/mL group.

Surgeons make a small, full-thickness scleral cutdown and photocoagulate the uvea once it is exposed. The vitreous is entered with a 3.2-mm blade, and the filled device is then inserted.

"The implant fits securely in the sclera and the only sutures needed are for closing the overlying conjunctiva," Dr. Regillo said.

Implant refilling is an office-based procedure performed using a proprietary needle inserted into the device through the conjunctiva.

"From the patient’s standpoint, the postoperative care and recovery from the implantation is similar to that of patients undergoing cataract surgery with the use of eye drops for a few weeks and relatively quick healing, and for the refill procedure, the patient experience is similar to an in-office intravitreal injection in terms of being well-tolerated, but it takes a bit more time to perform," Dr. Regillo said.

ARCHWAY, a phase III study comparing PDS 100 mg/mL refilled every 24 weeks with monthly intravitreal ranibizumab 0.5 mg, was launched in September 2018 and has a planned enrollment of 360 patients.

"We are very excited to see the first true sustained-release platform for an anti-VEGF agent making it into the pivotal trial phase," he said.

"This is a large study with many participating centers, and great effort is being made to optimize safety through extensive training of new investigators," Dr. Regillo added.

CARL REGILLO, MD
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Dr. Regillo receives research grant support from and is a consultant to Genentech.
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Ophthalmology Times
The Division of Ophthalmology at the University of Vermont College of Medicine, in alliance with the University of Vermont Medical Center, is seeking an academic neuro-ophthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency or a 3-year neurology residency and a clinical neuro-ophthalmology fellowship, and be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The successful applicant will be appointed at the Assistant/Associate Professor level in the Clinical Scholar Pathway, commensurate with years of experience and accomplishments.

Duties will include providing clinical care to neuro-ophthalmology patients, teaching the principles of ophthalmology to medical students and undergraduate students in Allied Health programs, providing teaching experience for residents in training, developing basic and/or clinical research, and performing additional departmental and/or sectional administrative duties as assigned by the Chair of the Department of Surgery.

This is a full-time, 12 month, salaried, faculty appointment and carries with it attending staff privileges at The University of Vermont Medical Center. Salary is competitive and commensurate with ability and experience.

Located in Burlington, the University of Vermont Medical Center serves as Vermont’s only academic medical center. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

Interested individuals should apply online at https://www.uvmjobs.com/postings/32453 (position number 006035). Inquiries may be directed to Dr. Brian Kim c/o Kathryn Raymond at Kathryn.Raymond@uvmhealth.org.
By Alan B. Richards, MD; Special to Ophthalmology Times

It takes a village: Vision screening via collaboration

Pediatricians, school nurses can easily administer visual-screening tests among children

When I first arrived in Louisiana more than 30 years ago, I was the state’s only pediatric ophthalmologist. Early on, I was interested in enhancing methods of visual acuity testing and screening for the community’s children. By 1981, I had helped to develop the state’s school vision-screening guidelines and found myself as de facto head of vision screening in Louisiana.

Along with my colleague, Carolyn Phillips, a trained vision screener, we have worked for decades to educate local pediatricians, family practitioners, and school nurses to the importance of early childhood vision screening. We also collaborate closely with the Lions Clubs.

Long-standing recommendations from various professional societies and organizations have called for young children to be evaluated to identify those with visual defects, and for those determined to be at risk to be referred to a pediatric ophthalmologist.

The rate at which these recommendations are being implemented into daily practice, however, remains less than ideal. As many as 15% of children have risk factors for amblyopia, yet fewer than 20% of children receive adequate screening.1,2

Performing traditional visual acuity testing on children is time consuming, occupies a nurse or technician for several minutes, and may be inaccurate. A vision check often includes a red reflex examination with an ophthalmoscope and a visual acuity test.3

Ophthalmoscopy may not be sufficient to determine if amblyopic risk factors are present, and deprivational and refractive amblyopia are more difficult to find using an ophthalmoscope.4 Studies have also shown that there is a 0% positive predictive value for traditional visual acuity testing when children are 3 to 4 years old.3

Photoscreening, on the other hand, has been shown to be a better option, with the best evidence in kids ages 3 to 5 years.4,5

We currently recommend a vision-screening device (plusoptiX) to our community partners. The device not only screens for refractive error, but also picks up things like media opacities, ptosis, and unequal pupils.

Although there is less evidence associated with the device’s use in children 6 months to 3 years of age, it will identify those who need early treatment, such as patching or glasses.

Device-based vision screening is extremely valuable in children with special needs and those who are developmentally delayed or nonverbal.

The device’s settings must account for the population and age group, as younger children will have more false positives. Most fail due to astigmatism; therefore, in our community we have encouraged pediatricians to use a setting of 3 D with plusoptiX.

Our program is effective through our grassroots and collaborative approach. By educating key members of the community—primary-care doctors, school nurses, and the Lions Clubs—to the importance of early childhood vision screening, we ensure they are engaged and aware of the need. By then being available to answer questions, address concerns, and visit locations to evaluate their individual vision-screening processes, we can help ensure no child falls through the cracks.

One pediatric ophthalmologist has spent 30 years educating the Louisiana community’s stakeholders about the importance of vision screening for young children.

Methods of outreach

I partner with an optometrist colleague, and together we go into the community and talk to pediatricians, evaluate their screening setup, and answer their questions about any issues they have. This grassroots approach has been effective in our area.

We have also worked with local representatives to pass legislation, where appropriate, to facilitate proper vision screening. Louisiana does not have a mandate requiring proof of a vision screening before a child begins school. The Medicaid program, however, which covers about half of the children in the state, requires a vision screening as part of many health tests for those ages 6 months to 5 years.

I believe that, requiring a full vision exam is wasteful and not an effective approach for our state. A potential result would be many children receiving exams from providers who are not specialists in children’s eye care and being prescribed unnecessary glasses.

This sort of inefficiency causes parents and caregivers to become frustrated with the entire process. Legislation in this capacity would require the necessary groundwork that ensures compliance with the law as well as funding for such an initiative. This approach is not a good fit for Louisiana, although it may work other in other states.

Conclusion

Device-based screening is extremely valuable in children with special needs and those who are developmentally delayed or nonverbal.

The device’s settings must account for the population and age group, as younger children will have more false positives. Most fail due to astigmatism; therefore, in our community we have encouraged pediatricians to use a setting of 3 D with plusoptiX.

Our program is effective through our grassroots and collaborative approach. By educating key members of the community—primary-care doctors, school nurses, and the Lions Clubs—to the importance of early childhood vision screening, we ensure they are engaged and aware of the need. By then being available to answer questions, address concerns, and visit locations to evaluate their individual vision-screening processes, we can help ensure no child falls through the cracks.

To read the fully referenced article, go to OphthalmologyTimes.com/Village
Ocular Surface Disease (OSD) advantage in the clinic: Why preoperative care matters
Follow ocular surface disease protocol for most favorable cataract surgery outcomes

By Neel R. Desai, MD; Special to Ophthalmology Times

Preoperative treatment of ocular surface disease (OSD) is an asset that many cataract surgeons tend to undervalue. I often talk to peers who treat OSD as a nuisance that gets in the way of proceeding with the ultimate goal of cataract surgery, but for those of us who are outcomes-driven and see that those outcomes help build the reputation and goodwill we need to grow our practices, treating OSD prior to surgery is an important goal in itself.

If you think treating OSD before surgery is a burden, consider these numbers:

1. In Trattler’s landmark PHACO study,4 up to 76.8% of patients presenting for cataract surgery had some form of OSD. At least 50% of them had severe enough OSD central to the visual axis that could negatively affect surgical outcomes if it were left untreated.
2. In my own practice, I treated patients with epithelial basement membrane dystrophy affecting preoperative biometry with traditional dry eye therapies, superficial keratectomy, and placement of a cryopreserved amniotic membrane biologically active bandage (PROKERA, Bio-Tissue) for 5 days. After following this protocol, average Ks changed by at least 1D in 50% of patients and up to 2D in 19%. BCVA improved 1 to 2 lines. If we hadn’t treated the problem before surgery, inaccurate IOL powers would have led to refractive surprises after surgery.

By treating OSD, our practices accumulate better outcomes and happier patients, reduce costly postoperative chair time and enhancements, and get reimbursed for OSD treatment.

**PREOP CARE PROTOCOLS**

The first step is to get patients to understand the importance of treating OSD before surgery. I tell my patients: “I’d rather do this the right way than the fast way.” Based on the severity of OSD—mild, moderate, or severe—I follow a protocol to get the best outcome.

**Mild OSD:** The vast majority of my cataract patients with OSD have the mild form. A below-normal tear breakup time and clinical signs might indicate mild blepharitis, meibomian gland dysfunction (MGD), or superficial punctate keratitis (SPK). The traditional course of therapy (artificial tears, hot compresses, lid cleansers, and nutraceuticals) is usually enough to optimize the ocular surface.

If the patient’s OSD involves MGD, rosacea, or evaporative dry eye, I may use intense pulsed light (IPL) therapy (M22 Optima IPL, Lumenis) to reduce lid and eye area telangiectasia and break the vicious cycle of inflammation. I try to get in as many IPL treatments as I can before the cataract surgery (spaced 2 weeks apart), but I don’t hold up cataract surgery for the IPL series. If I am concerned about biometric accuracy due to OSD, I use PROKERA to reoptimize the surface rapidly for cataract planning.

**Moderate OSD:** These patients have mild corneal staining and mild to moderate blepharitis, SPK, or MGD. There may be topographic changes on the cornea, such as irregular islands, breaks of dropout where data are absent, or inconsistency between biometry modalities. The RMS value is below .4 and does not seem to affect the central 6-mm zone.

In addition to traditional therapies, I start these patients on a steroid taper, as well as an immunomodulator such as cyclosporine (Restasis, Allergan) or lifitegrast (Xiidra, Shire). I consider IPL, as well as thermal pulsation therapy (LipiFlow, Johnson & Johnson Vision) for more rapid treatment of MGD prior to surgery.

For patients with moderate keratitis—punctate epithelial keratitis (PEK) or SPK—I consider placing PROKERA for 3 to 5 days without a superficial keratectomy in the more severe eye, and then treating the second eye.

**Severe OSD:** Patients with severe OSD may have moderate to severe staining inside the 6-mm visual axis zone, significant topographical irregularities, pronounced inconsistency between modalities of biometry, an RMS value greater than .4, Salzmann nodular degeneration, or recurrent erosion syndrome.

I follow the same treatments as mild and moderate OSD, while adding other appropriate therapies. For example, I may combine treatments, following thermal pulsation therapy with IPL. For some patients, I combine superficial keratectomy with PROKERA. Not only is the intensity of treatment higher for severe OSD, but it also requires more time for therapies to produce optimal results.

Hence, it is important to impress upon patients the value-added benefit of this optimization process in terms of better, more accurate outcomes and greater breadth of choice in lens implant opportunities.

**OUTCOMES AND POSTOP CARE**

Postoperative care for OSD begins before surgery, when we teach patients that the problem is chronic and requires long-term treatment.

My patients have a long-term plan before surgery, which usually involves continuing traditional at-home therapies and prescription medications. If they have had thermal pulsation therapy and/or IPL, they will return for follow-up sessions, which usually taper to once per year.

In our practice, we have seen that optimizing the ocular surface elevates patient satisfaction and word-of-mouth referrals. It also boosts our rates of refractive cataract surgery.

Before treating OSD, we would offer refractive surgery to about 50% of cataract patients, but after treatment, that number rises to about 90%.

When our patients have better vision and our practice is growing, we can’t look at treating OSD as a nuisance—it is most definitely an opportunity.

**Reference**


**NEEL R. DESAI, MD**

pc: 727-344-3008
Dr. Desai is director of Cornea, Cataract, and Refractive Services at The Eye Institute of West Florida; medical director, Lions Eye Institute for Transplant Research; and president and CEO, Clarity Visionary Consulting. He is a consultant to Allergan, BioTissue, Lumenis, Johnson & Johnson Vision, and Shire.
Don’t split hairs when it comes to subspecialties

“AOP conference 2019

You're correct! How did you guess that I’m a pediatric ophthalmologist?”

Artwork by Jon Carter

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**USE IN SPECIFIC POPULATIONS**

**Pregnancy**  
Pregnancy Category C

Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (i.v.) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD)), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at all i.v. doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at i.v. doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of > 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preupal separation, and by decreased motor activity.

There are no adequate and well-controlled studies of** **TRAVATAN Z® (travoprost ophthalmic solution)** **0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **TRAVATAN Z®** Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **TRAVATAN Z®** Solution is administered to a nursing woman.

**Pediatric Use**

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

**Geriatric Use**

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

**Hepatic and Renal Impairment**

Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 160 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 62 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat liver S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day (250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)). At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

**PATIENT COUNSELING INFORMATION**

**Potential for Pigmentation**

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **TRAVATAN Z®** (travoprost ophthalmic solution) 0.004%.

**Potential for Eyelash Changes**

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **TRAVATAN Z®** Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

**Handling the Container**

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

**When to Seek Physician Advice**

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have corneal surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **TRAVATAN Z®** Solution.

**Use with Contact Lenses**

Contact lenses should be removed prior to instillation of **TRAVATAN Z®** Solution and may be reinserted 15 minutes following its administration.

**ADVERSE REACTIONS**

**Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with **TRAVATAN Z®** (travoprost ophthalmic solution) 0.004% and **TRAVATAN Z®** (travoprost ophthalmic solution) 0.004% ocular hypotensive was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with **TRAVATAN** or **TRAVATAN Z®** Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1% to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostatitis disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, perianal and lid changes including deepening of the eyelid sulcus have been observed.
Intraocular Inflammation of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Hair in the treated eye. These changes include increased length, thickness, and number during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Macular Edema—Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma—TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

**INDICATIONS AND USAGE**

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% 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. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP lowering effect. TRAVATAN Z® Solution 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 5 minutes apart.

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

- Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, 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. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.
- Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.
- Intraocular Inflammation—TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.
- Macular Edema—Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution 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.

**Adverse Reactions**

- Bacterial Keratitis—There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
- Use with Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.
- Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

**For additional information on TRAVATAN Z® Solution, please refer to the Brief Summary of Prescribing Information on the following page.**

*Study Design: Double-masked, randomized, parallel-group, multicenter noninferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) and TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Mean baseline IOPs were 27.8 mm Hg (n=320), 23.5 mm Hg (n=322), and 24.8 mm Hg (n=320) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of month 3, the TRAVATAN Z® Solution group had mean IOPs (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistically equivalent reductions in IOP (95% CI about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

INDICATION FOR USE.
The iStent inject® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS.
The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrolubular tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

WARNINGS.
Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

MRI INFORMATION.
The iStent inject is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details.

PRECAUTIONS.
The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoequlatorial, pigmentedary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS.
Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

REFERENCES:
1. iStent inject® Trabecular Micro-Bypass System: Directions for Use, Part #45-0176.

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