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Moving the Mercury: Managing IOP via Dual-action Therapy

A ROUNDTABLE DISCUSSION

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Anaheim, CA

PARTICIPANTS

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INTRODUCTION

Glaucoma is a leading cause of irreversible blindness worldwide.[1,2] The estimated number of people living with glaucoma globally is around 70 million; of these, more than 70% are affected by open-angle glaucoma (OAG).[1,2] The predominant type of glaucoma in North America is primary OAG (POAG), which affects about 3% of the population between 40 and 80 years of age.[2] The frequency of POAG increases with age.[3] An estimated 2.71 million Americans had POAG in 2011; the projected number of diagnosed patients by 2050 is 7.32 million.[4]

POAG progresses inevitably in the absence of treatment, and the only treatable risk factor is intraocular pressure (IOP). In the healthy eye, IOP is regulated by the balance of aqueous humor production at the ciliary body and outflow through two routes—the trabecular (ie, conventional) and uveoscleral (ie, nonconventional) pathways.[5] In patients with POAG or ocular hypertension, chronic cellular contraction and increased extracellular matrix deposition within the trabecular (conventional) outflow pathway results in reduced aqueous humor outflow, which causes IOP elevation.[5-7] It is believed that high IOP levels cause progressive damage to the optic nerve, resulting in vision loss.[5] A number of other risk factors for OAG have been identified, including increasing age, as mentioned above; but also race (Black and Hispanic patients are at higher risk), larger optic disc or more extensive cupping of the disc, and a thin cornea.[3] However, IOP is the only modifiable risk factor for the development and progression of OAG, and so the reduction of IOP continues to be the solid and proven basis of both medical and surgical management.[3]

A substantial body of research has shown that IOP reduction is effective in managing OAG. The Ocular Hypertension Treatment Study was the first large-scale study to demonstrate that lowering IOP can safely delay POAG.[8] Since then, many other studies have proved the effectiveness of IOP reduction in delaying the progression of glaucoma.[9-13] In the Early Manifest Glaucoma Trial, treated patients had half of the progression risk of those in the untreated control group after a median follow-up of 6 years.[11] In the Advanced Glaucoma Intervention Study, patients whose IOP was lower than 18 mm Hg IOP on all visits over 6 years demonstrated almost no visual field loss.[9]

Prostaglandin analogs (PGAs) are typically the initial choice for treating OAG because they are effective, have a demonstrated safety profile, and are dosed once daily. Furthermore, as people age, outflow through the conventional and uveoscleral pathways is diminished,[14] which often requires additional IOP-lowering. This leads to a continued need for new therapies that can lower IOP.

This supplement presents the highlights of a roundtable discussion on medical IOP-lowering therapies among a panel of six optometric glaucoma specialists. We come from all over the country, with different patient populations and from a range of institutional settings, including a large university clinic, private practices of differing sizes, and a VA hospital. But in all cases, roughly 50% of our patients have glaucoma. In other words, we are intimately familiar with this sight-threatening disease.

One of the main goals of our roundtable discussion was to provide an informative introduction and guide to Vyzulta™ (latanoprostene bunod ophthalmic solution) 0.024%, a novel PGA that is designed to act through two moieties: latanoprost acid and butanediol mononitrate, which releases nitric oxide (NO). We describe the main features and mechanism of action (MOA) of this drug, and then explore the ways it might be used to benefit our patients and our practices.

— Murray Fingeret, OD

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin F2α analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect.

If VYZULTA™ is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart.

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SETTING A TARGET IOP

MURRAY FINGERET, OD What are your considerations when choosing a patient's target IOP, and what is your approach to treatment modification during the course of therapy?

RON MELTON, OD I establish a patient's target IOP based on their individual risk factors: peak IOP, optic nerve cupping, visual field findings, retinal nerve fiber layer analysis, corneal thickness, positive family history, and ethnicity. All of these risk factors allow me to determine a target range for a particular patient. For example, if a patient has a more advanced case of glaucoma, I am looking for a target pressure in the low teens. For moderate glaucoma, the mid-teens may be an acceptable target range. If there is mild glaucoma that is stable or I decide to treat an ocular hypertensive patient, then the upper teens or even higher may be an acceptable IOP.

FINGERET Does anyone look for a specific number or percent reduction?

RANDALL THOMAS, OD, MPH The literature has shown that if IOP can be reduced by about 25%, the rate of progression will be dramatically decreased, so that is what I aim for.[3] As Dr. Melton noted, family history is a very strong risk factor. It's also important to look at the patient's age, health status, and any other medications they are taking, such as systemic beta blockers.

FINGERET I look at the target pressure as simply being a starting point. Over time, I repeatedly perform visual fields, do imaging, and look at the optic nerve and retinal nerve fiber layer (RNFL) to determine if the patient is stable. If the patient is not stable, then I know I'm not at the target pressure—even if I had hit my initial goal—and I modify therapy.

BEN GADDIE, OD As has been mentioned, risk assessment is important for determining the patient's likelihood for having functional vision loss and glaucoma. For patients who have moderate to severe glaucoma, I set a more aggressive target pressure than for those who have ocular hypertension or mild, early glaucoma. If I see patients progressing, that tells me they are not at their target pressure.

PINAKIN DAVEY, OD For me, the key to determining target pressure range is to first classify the glaucoma. If I know that I am dealing with high-pressure POAG, then I can estimate at what pace it might progress. For normal tension glaucoma (NTG) patients, I try to do a modified "diurnal pressure estimation" on them. If it's a narrow-angle glaucoma, then we manage it a bit differently. After classifying the glaucoma, I then assess the risk with all the values that we know—such as corneal thickness, race, and age—and come up with an IOP range.

FINGERET Does anyone else do diurnal pressures? How much does IOP fluctuate during the day and night, and is IOP fluctuation an independent risk factor for glaucoma progression?

DEREK CUNNINGHAM, OD I think IOP fluctuation is an independent risk factor, and this is supported by a number of studies.[15-17] In the Advanced Glaucoma Intervention Study, an increase in IOP fluctuation of 1 mm Hg was associated with a 30% increased risk for visual field loss.[16] Of course, normal IOP might go up and down 4 mm Hg to 6 mm Hg over the course of a day; and I would only consider changing treatment based on very large fluctuations for an individual patient.

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GADDIE From sleep studies, we know that being in the supine position at night can cause significant increases in IOP, which also might contribute to the pathogenesis of glaucoma.[18]

MELTON The degree of IOP fluctuation can vary from patient to patient. Some of the fluctuation seen in an individual may be due to medications the patient is taking.[19]

THOMAS Because it's not clear to me how much IOP fluctuation, in and of itself, contributes to the risk for glaucoma, I think the key is to try to determine what the peak IOP is for a patient. That's why it's important to check pressures at different times of the day.

SELECTING TREATMENT

GADDIE **How would you characterize the currently available classes of glaucoma medicine in terms of MOA, and how do you go about selecting treatment?**

DAVEY Beta blockers lower IOP by decreasing aqueous humor production.[3]

THOMAS Alpha-2 agonists predominantly decrease aqueous.[3] The only alpha-2 agonist that we use in my practice is brimonidine, an alpha-2 selective agonist. It may enhance aqueous outflow in addition to decreasing aqueous production, but its full MOA is still not completely understood.[3]

GADDIE Topical carbonic anhydrase inhibitors (CAIs) reduce the production of aqueous humor, predominantly.[3]

THOMAS The heart of aqueous humor dynamics is in the hindrance of aqueous outflow, and the miotic pilocarpine addresses that.

CUNNINGHAM Importantly, pilocarpine works on the trabecular meshwork (TM), and the TM accounts for 60% to 80% of aqueous outflow in healthy human eyes.[20]

CUNNINGHAM PGAs work primarily by increasing uveoscleral (nonconventional) outflow, but some PGAs may also target the TM.[3] They upregulate matrix metalloproteinase activity within the uveoscleral pathway, and this increases the interstitial spaces between the ciliary muscle bundles to allow for greater aqueous humor outflow.[5,21]

The TM accounts for 60% to 80% of aqueous outflow in healthy human eyes. —*DEREK CUNNINGHAM*

GADDIE Given that most of the drugs we have discussed either decrease aqueous production or primarily target the uveoscleral pathway, I think we have an unmet need for drugs that target the TM.

GADDIE **PGAs are a common first-line treatment. What are the features of PGAs? Are there circumstances where you might not choose a PGA as initial therapy for your patients that need to be treated?**

DAVEY PGAs are effective IOP-lowering agents. They are also dosed once daily.

THOMAS My common practice is to initiate therapy with a topical PGA. However, there are some patients for whom this might not be best, such as patients with chronic recurrent anterior uveitis or chronic recurrent cystoid macular edema.

GADDIE There is also a risk for patients that have had traumatically ruptured posterior capsule during cataract surgery—that would also be a contraindication for a PGA.

CUNNINGHAM I avoid PGAs in proliferative diabetic retinopathy patients because it's an inflammatory glaucoma disorder.

IMPORTANT SAFETY INFORMATION

- 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

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MODIFYING TREATMENT

GADDIE **What proportion of patients in your practice require more than one medication to achieve or maintain the desired target range?**

FINGERET In the Ocular Hypertension Treatment Study, where the goal of treatment was to reduce the pressure by 20%, about 60% of patients could be controlled with one medication, but 40% needed two or more. Within that 40%, 9% needed three medications.[8] This suggests that it is unlikely that a target pressure of 18 mm Hg or less can be achieved with just one PGA. When you have someone on a PGA but they need more pressure lowering, do you try a different medication, such as a different PGA, or do you add a medication, or something else?

GADDIE It depends on the risk assessment of the patient. For patients who are ocular hypertensive or have mild glaucoma, I might see if they can be stabilized at that particular pressure. If they have moderate to severe glaucoma, then it's possible the patient is a PGA nonresponder. In that case, I might replace it with a combination medicine or consider laser trabeculoplasty.

MELTON In my experience, within 2 to 5 years, 40% to 50% of my patients will need a second medication to control their IOP. However, one's strategy for adding a second medication depends to some degree on the make-up of one's practice. For example, in the African-American population, IOPs tend to run higher and their glaucoma can progress faster.[22,23] As a result, I am likely to add a second medication sooner in that demographic.

THOMAS I think we're starting to recognize that we now have the technology to monitor progression, thanks to optical coherence tomography and advanced perimetry. We are able to acquire information earlier than we used to for indicating that we might need to modify therapy.

CUNNINGHAM If I don't get adequate control with one PGA, I often use an alpha-2 agonist as my adjunct. But my practice patterns have changed dramatically in the last 3 years. I used to aggressively reach for adjunctive therapies, but now I consider a surgical approach more often than in the past.

MELTON As monotherapy, the PGAs reduce pressure on average from 25% to 33%, while the beta blockers and alpha-2 agonists reduce pressure 20% to 25%.[3] So it makes common sense to the average eye care provider to add a medication rather than to switch to a class that reduces IOP less than the PGAs.

THOMAS The pivotal concern here is how much reduction in IOP was achieved with the PGA. If I achieved 20%, I consider that somewhat of a success—and if that doesn't get me to the target IOP, then I would consider adding a different class of drug.

GADDIE **I think there is some value, depending on the original PGA the patient was prescribed, in switching to a different one. In terms of adding an agent, do you typically go to a single agent adjunctive medication or to a combination?**

DAVEY If the patient is absolutely a nonresponder, then I would go to another class of drug, unless I suspect that the patient just hasn't been using the medication at all. But I don't jump to combination therapy. If I have some amount of lowering, such as 20%, I would add a second drug.

CUNNINGHAM I don't like adding combinations, because I don't know which part of the combination is working. I mostly go to a single adjunct first. If I need something on top of that single adjunct, and that adjunct is available in a combination, then I might consider using the combination—in part because decreasing the number of drops is important to me.

MELTON I also typically add a single agent as my second drop. In 35 years of clinical practice, I have seen that adding that second single agent will perform well for many years.

GADDIE **In my experience, if a patient needs an adjunctive drug, the chance that they are going to need a second adjunctive drug in the short-term is pretty high. Therefore, I have been switching to combinations fairly frequently. When you add a single agent adjunct, what's your expected additional IOP reduction on top of a baseline PGA?**

DAVEY I have noticed, in my practice, that when added to a PGA, the other IOP-lowering drugs—alpha-2 agonists, beta blockers, or CAIs—can give around 15% reduction, which often gets me to my target pressure range.

MELTON In treating an advanced glaucoma patient, we may want to be aggressive with the additional medication and consider a combination glaucoma product after a PGA. If we are wanting to reduce our target pressure a couple of points in a mild glaucoma patient, then a single agent should work fine.

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DUAL-ACTION THERAPY

GADDIE **Vyzulta™ (latanoprostene bunod ophthalmic solution) 0.024% is a novel PGA that is designed to act through two moieties: latanoprost acid (which enhances uveoscleral outflow), and butanediol mononitrate (which releases nitric oxide) (Figure 1). What do we know about the mechanism of action of Vyzulta, and about the physiological functions of nitric oxide (NO)?**

THOMAS Latanoprost acid enhances uveoscleral outflow. As an endogenous signaling molecule generated by a family of enzymes called NO synthases (NOS), NO has effects all over the body. We have known for some time that NO can be beneficial to blood flow in different parts of the body, including in the eye.[24]

CUNNINGHAM NO also increases the dilation of blood vessels through vascular smooth muscle relaxation,[25] which can have beneficial effects in terms of bringing important proteins and hormones to organs, including the eye.[24]

DAVEY In addition, NO alters the contraction of smooth muscle. As an IOP-lowering agent, NO acts primarily on the TM and Schlemm's canal, helping to open up and facilitate aqueous outflow.[24,26]

Vyzulta™ (latanoprostene bunod ophthalmic solution) 0.024% acts to increase uveoscleral outlow and relax the TM to improve trabecular outflow in a single agent.

—PINAKIN DAVEY

GADDIE NO is produced endogenously in the eye, in small amounts. There is some basic science research that supports the role of NO in glaucoma, including studies showing that glaucomatous eyes have evidence of less NO than non-glaucomatous eyes.[27,28]

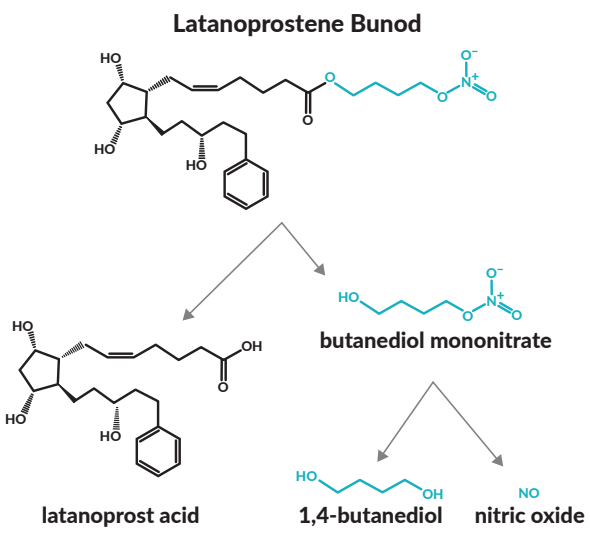

FIGURE 1 Chemical structure and metabolism of Vyzulta™ .

FINGERET A series of bench studies showed that in cultured human TM cells, NO had a beneficial effect at the juxtacanalicular region, which lies adjacent to Schlemm's canal and is the area of the TM implicated in establishing IOP. This is where much of the outflow resistance is.[29-31] NO seems to open up spaces within the TM to allow aqueous to more easily flow out. By activating the NO-soluble guanylate cyclase–cyclic guanosine-3',5'-monophosphate (NO-sGC-cGMP) signaling pathway, NO induces cell relaxation and thus a widening of intercellular spaces in the TM.[24,25,32,33]

DAVEY PGAs work primarily by increasing uveoscleral outflow: they relax the ciliary muscle and alter the extracellular matrix of the ciliary body to make it more responsive to aqueous outflow.[20,34] NO relaxes the TM to increase the outflow facility through the TM, the juxtacanalicular tissue, and Schlemm's canal, which together provide most of the aqueous humor outflow resistance.[29-31] Vyzulta™ enhances uveoscleral and trabecular outflow in a single agent (Figure 2).

IMPORTANT SAFETY INFORMATION

- 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

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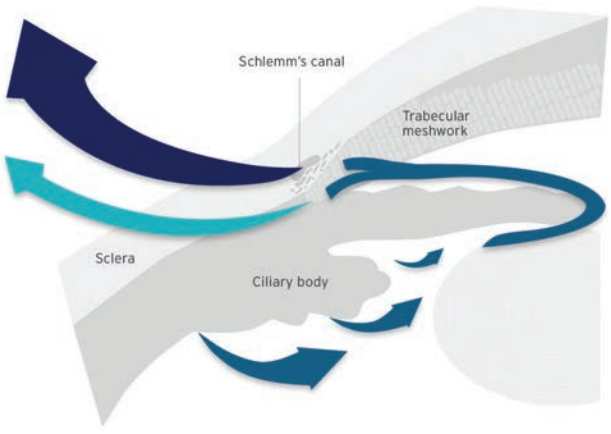

FiGURE 2 Vyzulta™ works on the uveosceleral and trabecular outflow pathways.

VYZULTA™: KEY FEATURES

IOP-LOWERING EFFICACY

FINGERET What stands out to you from the clinical trials for Vyzulta™ regarding efficacy and duration of effect?

MELTON In two phase 3 multicenter, randomized, prospective, double-masked, parallel-group studies—APOLLO (N = 418) and LUNAR (N = 415)— Vyzulta™ produced an IOP reduction of 7.5 to 9.1 mm Hg from baseline between week 2 and month 3 in patients with OAG or ocular hypertension (Table I). IOP reduction with Vyzulta dosed once daily at night was non-inferior to that with timolol 0.5% dosed twice daily. Vyzulta demonstrated superiority over timolol at month 3 in both studies, with an additional 1.2 mm Hg reduction in mean diurnal IOP.[36,37] That IOP reduction from 7.5 to 9.1 mm Hg really stood out to me. I was very impressed with that level of IOP reduction. In the phase 2, dose-ranging VOYAGER study, Vyzulta™ lowered IOP by 9.0 mm Hg from baseline—a statistically significant, additional 1.2 mm Hg over latanoprost 0.005% (P = 0.005)—after four weeks in patients with OAG or ocular hypertension.[35]

FINGERET How impactful is an extra 1 mm Hg of IOP reduction?

THOMAS The Early Manifest Glaucoma Trial showed that each 1 mm Hg reduction of IOP was associated with a 10% decrease in the risk of progression, and that the reduction in risk may be up to as high as 19% for a 1 mm Hg reduction in IOP.[10] The bottom line is that every millimeter counts.

DAVEY I want to add that 1 mm Hg in a population sample is a lot. Individual results can of course vary, but for a population to still show that mean difference is significant.

MELTON Regarding duration of effect, in the phase 3, single-arm, multicenter, open-label JUPITER study (N = 130), treatment with Vyzulta™ reduced IOP significantly in a group of Japanese patients with OAG or ocular hypertension—and this reduction was sustained

TABLE I Change from baseline in mean IOP in APOLLO and LUNAR study

	Week 2			Week 6			Month 3		
	8 am	12 pm	4 pm	8 am	12 pm	4 pm	8 am	12 pm	4 pm
APOLLO									
LBN mean CFB (mm Hg)	−9.0	−8.5	−7.7	**−9.1**	−7.9	−9.0	−8.7	−7.9	
Timolol mean CFB (mm Hg)	−7.8	−7.2	−6.6	−8.0	−7.4	−6.7	−7.9	−7.4	−6.6
Treatment difference	**−1.21**	**−1.37**	**−1.11**	**−1.03**	**−1.24**	**−1.26**	**−1.02**	**−1.27**	**−1.33**
P value	<0.001	<0.001	<0.001	<0.002	<0.001	<0.001	<0.002	<0.001	<0.001
LUNAR									
LBN mean CFB (mm Hg)	−8.3	−8.1	**−7.5**	−8.8	−8.5	−7.8	−8.8	−8.6	−7.9
Timolol mean CFB (mm Hg)	−7.9	−7.3	−6.9	−7.9	−7.7	−6.8	−7.9	−7.4	−6.6
Treatment difference	**−0.44**	**−0.76**	**−0.69**	**−0.92**	**−0.84**	**−0.98**	**−0.88**	**−1.29**	**−1.34**
P value	0.216	0.022	0.025	0.005	0.007	0.003	0.006	<0.001	<0.001

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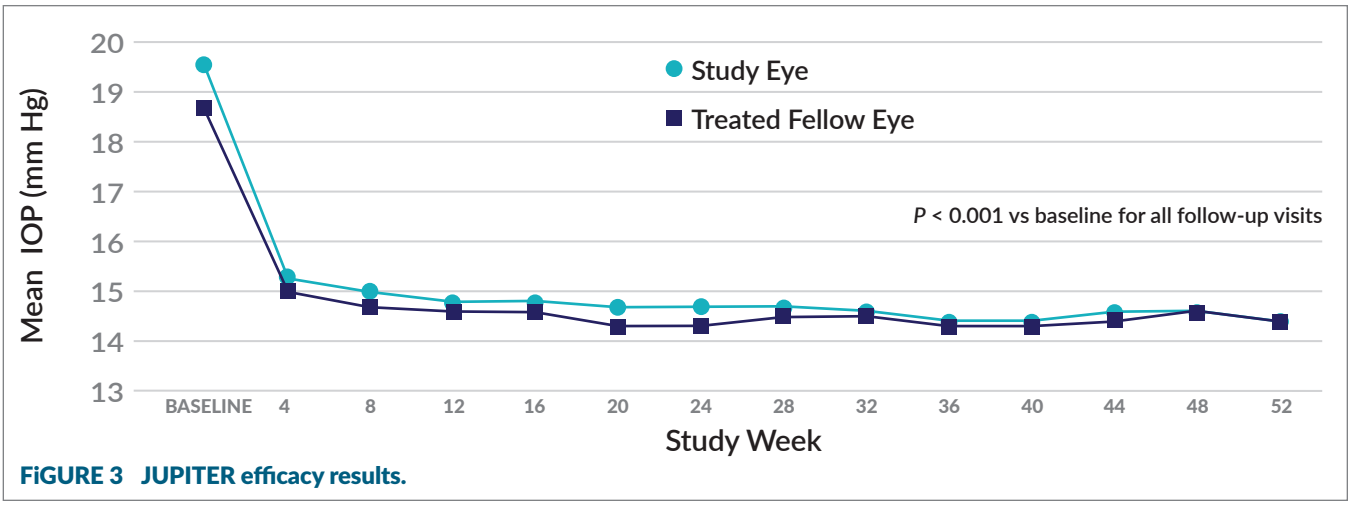

FIGURE 3 JUPITER efficacy results.

through week 52 (Figure 3).[38] These subjects had a notably low baseline IOP: 19.6 mm Hg on average for the study eye, and 18.7 mm Hg for the treated fellow eye.[38]

SAFETY AND TOLERABILITY

FINGERET What is notable about Vyzulta™ safety and tolerability?

GADDIE In the VOYAGER study, ocular treatment emergent adverse events (TEAEs) in Vyzulta™-treated eyes were similar to eyes treated with latanoprost, and all ocular TEAEs were mild or moderate in severity.[35]

FINGERET The pivotal trials of Vyzulta™ showed about 6% hyperemia.[39]

INCORPORATING VYZULTA™ INTO PRACTICE

FINGERET What do you find most exciting about Vyzulta™, and how do you foresee incorporating it into the continuum of care?

MELTON The fact that Vyzulta™ is a PGA that releases NO makes this an exciting product. A drug that can enhance uveoscleral outflow—the traditional PGA MOA—and also releases NO to improve TM outflow represents an exciting product in glaucoma therapy.

FINGERET We can look at IOP-lowering as falling into two camps: one is reducing the amount of aqueous being produced; and the second is enhancing outflow.

DAVEY Another reason I'm excited about Vyzulta™ is that in the JUPITER study, it lowered IOP up to 20% even when IOP was not significantly elevated to begin with.[38]

THOMAS Yes, and these patients without significantly elevated IOP can be up to 30% of the glaucoma patient population.

FINGERET What is your perspective on IOP lowering for NTG patients?

CUNNINGHAM If a patient is at 19 mm Hg, I'm usually looking to get the pressure down to 13 to 14 mm Hg. The lower the initial IOP, the harder it is to lower it further.

FINGERET Where do you envision Vyzulta™ fitting into your practice?

GADDIE First, I foresee using Vyzulta™ in patients with moderate to severe glaucoma for whom I want a good opportunity to have a low foundational pressure right off the bat. Second, I foresee using it with someone who is

IMPORTANT SAFETY INFORMATION

- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

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on a PGA but needs a little additional lowering, such as a single adjunct would provide.

THOMAS I would have no hesitation in using Vyzulta™ as a first-line therapy.

CUNNINGHAM Pending insurance coverage, Vyzulta™ will definitely be my first-line, almost exclusively.

FINGERET What about switching patients who are already on a single-agent PGA?

DAVEY I wouldn't change somebody who is already on a PGA and doing fine. I would consider switching a patient who is not responding adequately to another PGA to Vyzulta™ before adding an adjunctive therapy. For new patients, Vyzulta would be my starting point, without hesitation, given the solid safety results and lowering of IOP observed in various studies.

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Please see additional Important Safety Information on page 1 and continuing through page 8 of this advertisement, and Brief Summary of Prescribing Information for Vyzulta™ on page 11 of this advertisement.

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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 ophthalmic 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.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

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 are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation 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 pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for 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 had 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 in the clinical trials of another 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 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular 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, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension 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

Animal 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, on 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 ≥ 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, forepaw hyperextension 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 hyperextension 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 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 breastfed 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 rodent bioassays, was not carcinogenic.

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 toxicology 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 dose, bid. The systemic exposures are 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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