Controlling IOP in a Primary Open-Angle Glaucoma Patient Not at Target on Latanoprost

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VYZULTA®
(latanoprostene bunod ophthalmic solution),0.024%

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The art of managing glaucoma requires decision-making based upon a patient's full presentation, particularly as there is no standardized algorithm for predicting risk for progression or assigning treatment. Previously healthy patients without comorbidities may find a diagnosis of glaucoma difficult to accept and adherence to daily therapy challenging.

Clinicians can help patients adhere to treatment and follow-up by clearly outlining their risk factors (intraocular pressure [IOP]-related, genetic, corneal, etc), showing them the results of their imaging and visual field assessments, discussing options, and including them in decisions regarding starting or modifying treatment. The importance of taking their medications and attending follow-up appointments should be emphasized.[1]

The following case report describes a previously healthy 64-year-old male patient with a new diagnosis of primary open-angle glaucoma (POAG) and multiple risk factors for progression, including low corneal hysteresis (CH) and low central corneal thickness (CCT).[3-5] After weighing the pros and cons of several IOP-lowering strategies, the patient elected to switch from latanoprost to VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% in order to meet IOP-reduction goals.

CASE

BACKGROUND

Following a 4-year gap in care, a 64-year-old Caucasian male was found to have elevated IOP and a screening visual field (VF) defect during a comprehensive eye examination.

AT A GLANCE

- Factor intraocular pressure (IOP), disease stage, and corneal and genetic risk factors into target IOP calculations.[2]
- Low corneal hysteresis and low central corneal thickness have been associated with increased risk for progression.[3-5]
- Counseling regarding the importance of follow-up and the use of reminder systems can help newly diagnosed patients follow through.[6]
- All appropriate patients with open-angle glaucoma and ocular hypertension are good candidates for VYZULTA®. In my practice, we use VYZULTA for early, mild, moderate, and advanced glaucoma cases.

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

Please see additional Important Safety Information throughout and full Prescribing Information for VYZULTA® on pages 6-8.

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VYZULTA® IN PRACTICE:
CASES IN IOP-LOWERING

Murray Fingeret, OD

Glaucoma is a chronic, progressive, and potentially blinding disease, the burden of which increases as damage progresses.[1] Most therapies lower IOP by decreasing aqueous production or increasing uveoscleral flow—but do not increase conventional outflow[4] or necessarily provide the typical goal of 25% IOP reduction.[2] Often, these therapies do not target the diseased tissue—the trabecular meshwork (TM)—responsible for IOP increase.[3]

WHY VYZULTA®?

The first and only nitric oxide (NO)-donating prostaglandin monotherapy, VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% lowers IOP through a dual mechanism of action: increasing uveoscleral outflow via latanoprost acid, and increasing TM/Schlemm's canal outflow via NO-mediated relaxation of the TM.[4]

In phase 3 clinical trials, VYZULTA® showed consistent IOP lowering of 7.5 to 9.1 mm Hg from baseline;[5,6] in both these studies, VYZULTA® administered once a day in the evening was shown to be noninferior to timolol 0.5% twice a day in patients receiving over 3 months of therapy. VYZULTA® also demonstrated sustained IOP-lowering through 1 year in a pooled analysis of two randomized, double-masked Phase 3 studies[7] and a multicenter, single-arm Phase 3 study[8]; statistically greater IOP lowering > 1 mm Hg vs latanoprost 0.005% in a Phase 2 dose-ranging study [9]; robust 24-hour IOP control across a range of baseline IOPs in a phase 2, small cross over study, in addition to more IOP reduction and increased ocular perfusion pressure compared to timolol [10]; robust IOP-lowering in treatment-naïve patients [11]; and a safety profile consistent with the PGA class in a pooled analysis of pivotal phase 3 studies.[7] In a real-world retrospective chart review[11], in the subset of patients with higher IOP, mean (SD) percent reductions of 37.1 (13.8)% and 40.9 (13.4)% in IOP were observed at the first and second follow-up visits; in the subset of patients with lower IOP, mean (SD) percent reductions were 25.4 (18.1)% and 22.1 (15.2)% at the two follow-up visits.

CASES IN IOP-LOWERING

The cases in this series are real-life examples of optometrists using VYZULTA® in patients. Dr. Chaglasian describes a patient with low central corneal thickness and corneal hysteresis, newly diagnosed with open-angle glaucoma (OAG). Dr. Schweitzer's case involves a patient with normal-tension glaucoma. Dr. Sowka reports a case of a high myope diagnosed with early OAG.

I use VYZULTA® in the full range of patients with OAG and ocular hypertension—early, mild, moderate, and advanced—and across all pressure ranges.

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He was started on latanoprost one drop in both eyes once-daily and referred for a complete glaucoma evaluation.

His past ocular history was remarkable for elevated IOP on past examinations. Several years prior, the patient had completed screening visual fields and an OCT scan, both of which were normal. Due to perceived low risk of developing glaucoma, he was not treated at that time and follow-up visits were not kept. The patient also reported that his mother had glaucoma that was treated with eyedrops. Old records obtained from these past visits showed that the IOP (prior to treatment) was 32 mmHg on the right and 26 mmHg on the left. Most recently, he had been started on latanoprost daily at bedtime in both eyes.

DIAGNOSIS

At this consultation visit, the patient was fully evaluated for glaucoma, including ocular examination, fundus photos, OCT imaging, and VF testing. Best-corrected visual acuity (BCVA) was 20/20 in both eyes. IOP assessed by Goldmann tonometry (on latanoprost with last dose the prior eveing) was 24 mmHg on the right and 22 mmHg on the left. CCT was 500 microns on the right and 510 microns on the left; CH was 8.2 mmHg on the right and 9.3 mmHg on the left.

On the right, fundus photography revealed cup-to-disc ratio (CDR) of 0.4 horizontal, 0.5 vertical, with thinning and early notching to the superior temporal rim.

On the left, CDR was 0.3 (horizontal and vertical) with an intact neural retinal rim. An area of possible superotemporal retinal nerve fiber layer (RNFL) dropout was noted in the right eye. **(Figure 1)**

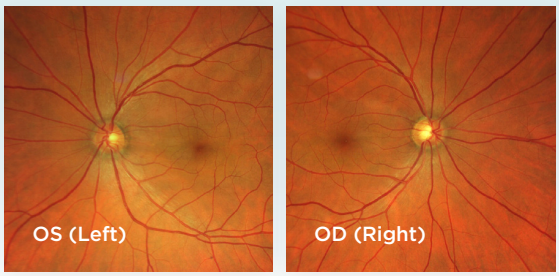


FIGURE 1

Optical coherence tomography (OCT) on the right showed a significant RNFL bundle defect in the superior temporal region, this is also seen on temporal-superior-nasal-inferior-temporal (TSNIT) plot. Ganglion cell complex showed diffuse thinning. Left eye OCT was within normal limits. **(Figure 2)**

Right eye VF testing revealed a partial arcuate defect and abnormal glaucoma hemifield test (GHT); visual field index (VFI) was 90%. The left VF was normal (except for isolated points in inferior nasal sector, possibly an artifact) with a VFI of 99%. **(Figure 3)**

The patient was diagnosed with primary open-angle glaucoma (POAG), severe stage, characterized by bilateral elevated IOP on treatment (right greater than left) and advanced, focal RNFL thinning and VF defect on the right. Risk factors for glaucoma development/progression included thin CCT, low CH, and positive family history of glaucoma.

TREATMENT

After approximately 2 months of latanoprost treatment, IOP had been reduced from 32 mmHg to 24 mmHg (a 25% reduction) on the right and from 26 mmHg to 22 mmHg (a 15% reduction) on the left. Based on his disease severity and risk factors, we wanted to achieve at least 35% to 40% reduction from pretreatment IOP.

One option was to continue latanoprost and add a second medication with a different mechanism of action, possibly an alpha agonist, a carbonic anhydrase inhibitor, a beta-blocker, or a rho kinase inhibitor.

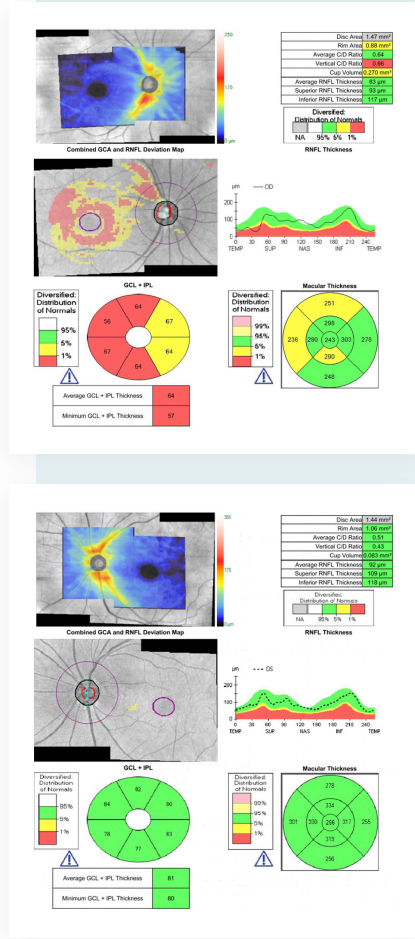


FIGURE 2

A second option was to maintain monotherapy and switch from latanoprost to VYZULTA®, since VYZULTA is the only prostaglandin analog (PGA) with a nitric oxide-releasing moiety.[7]

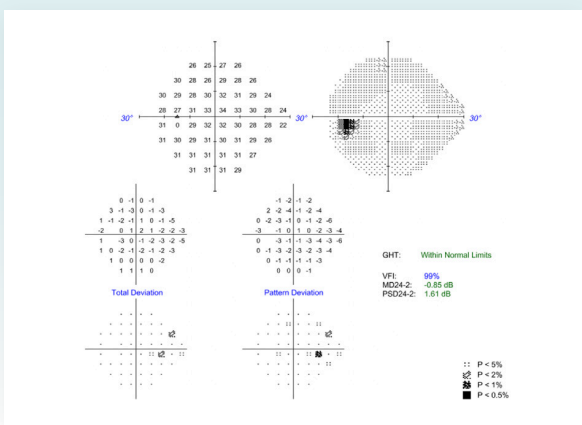
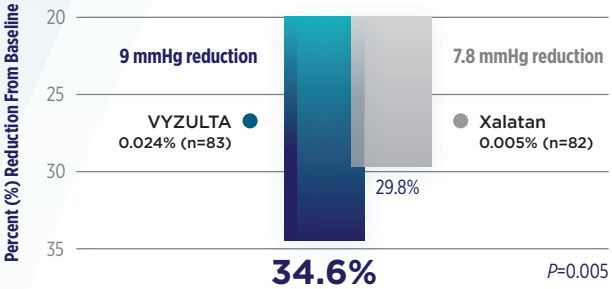


FIGURE 3 OS (Left) OD (Right)

STATISTICALLY GREATER EFFICACY VS XALATAN 0.005%[9,13]

VYZULTA® delivered significantly greater mean IOP reduction from baseline vs Xalatan 0.005% at Day 28[9]



Baseline Mean Diurnal IOP[9]

- VYZULTA 0.024%: 26.01 mmHg
- Xalatan 0.005%: 26.15 mmHg

~69% of VYZULTA patients achieved ≤18 mmHg mean diurnal IOP vs ~47% of Xalatan 0.005% patients[9]*

*Secondary endpoint. *P*<0.05.

FIGURE 4

A third option was to schedule the patient for selective laser trabeculoplasty (SLT) in an effort to avoid or minimize topical ocular therapy later. Starting treatment with SLT rather than drops may have benefits, including possibly reducing the need for surgery.[8]

Our patient elected to maintain monotherapy and switch to VYZULTA®, one drop in both eyes nightly.

WHY VYZULTA®?

The patient's lack of follow-through regarding elevated IOP in the past made me lean toward one of the latter two options, as I was concerned about nonadherence to a multi-drug regimen. I liked the patient's choice to try VYZULTA® to achieve further IOP reduction, since treatment with VYZULTA has been associated with greater IOP reduction than latanoprost in a direct comparison.[9]

Additional benefits of VYZULTA® included a straightforward dosing regimen (one drop once nightly each eye) and good tolerability in clinical trials.[10,11]

Regimens that patients can stick with—eg, those with a lower dosing burden and better tolerability—support adherence.[12]

FOLLOW-UP

At one month, the patient reported tolerating VYZULTA® without issue and was compliant with nightly treatment. IOP was significantly improved, 19 mmHg (a 40% decrease from baseline) on the right and 16 mmHg (a 38% decrease) on the left. In a phase 2 dose-ranging study, VYZULTA® delivered significantly greater mean IOP reduction from baseline vs Xalatan (latanoprost) 0.005% at Day 28: 34.6% for VYZULTA vs 29.8% for Xalatan. In addition, 69% of VYZULTA patients achieved ≤18 mmHg mean diurnal IOP vs ~47% of Xalatan 0.005% patients.[9,13] **(Figure 4)**

The patient was instructed to continue with VYZULTA® and counseled regarding the importance of follow-up care and maintaining target IOP.

CORNEAL HYSTERESIS

Corneal hysteresis is the ability of the cornea to absorb and release energy when acted upon by a force.[14,15] Studies in normal eyes have revealed a normal CH range of about 10.1 to 10.7 mmHg.[14,15] Lower CH has been associated as a risk factor for glaucoma. CH has been shown to be significantly lower in patients with NTG than normal eyes[16] and directly associated with significantly worse mean RNFL thickness in patients with NTG versus normal eyes.[17] Low CH has been shown in multiple studies to be an independent risk factor for the development and progression of glaucoma, making it a useful parameter (possibly more so than CCT) for glaucoma screening and clinical decision-making.[15,18-21] **(Table 1)**

TABLE 1. CORNEAL BIOMETRICS

	Average Range In Normal Eyes	Range in POAG	Patient Case (OD/OS)
CCT (micrometers)	537-554*	Low	500/510
CH (mmHg)	9.6-10.7**	8.0-10.0	8.2/9.3

CCT, central corneal thickness. CH, corneal hysteresis.

*AAO.org. Clinical Measurement of Intraocular Pressure https://www.aao.org/bcscsnippetdetail.aspx?id=5244feeb-13d6-4475-a224-b6ed97f492b3

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CLASSIFYING VISUAL FIELD (VF) DEFECTS

The landmark Ocular Hypertension Treatment Study followed (VF) changes every 6 months for more than 7 years among 1,636 patients with ocular hypertension. More than 38,000 follow-up tests were performed, which allowed researchers to distinguish VF abnormalities associated with glaucoma from those associated with other processes or artifacts.[22]

A VF abnormality fit the definition for glaucoma if the glaucoma hemifield test was outside of normal limits and/or there was a corrected pattern standard deviation with $P<0.05$. From most to least common, partial arcuate, paracentral, nasal step, arcuate, temporal wedge, and altitudinal defects were consistent with glaucoma. If a hemifield abnormality was present in one eye, and the other eye was without a hemifield defect but showed an abnormal cluster of points, VFs in both eyes were considered abnormal.

CONCLUSION

Goal of 30% to 40% reduction from pre-treatment IOP was achieved after switching this 64-year-old patient with newly diagnosed POAG (severe in one eye) from latanoprost to VYZULTA®.

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IMPORTANT SAFETY INFORMATION (CONT'D)

- 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
- 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%)

VYZULTA®
(latanoprostene bunod ophthalmic solution),0.024%

Please see additional Important Safety Information throughout and full Prescribing Information for VYZULTA® on pages 6-8.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do 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

---------- INDICATIONS AND USAGE ----------
VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- DOSAGE AND ADMINISTRATION ----------
One drop in the affected eye(s) once daily in the evening. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Topical ophthalmic solution: 0.24 mg/mL latanoprostene bunod (0.024%) (3)

----------CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pigmentation: Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash changes: Gradual changes to eyelashes including increased length, increased thickness and number of eyelashes. Usually reversible upon discontinuation of treatment. (5.2)

---------- ADVERSE REACTIONS ----------
Most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2019

FULL PRESCRIBING INFORMATION:
CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 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.

3 DOSAGE FORMS AND STRENGTHS

VYZULTA is a topical ophthalmic solution containing latanoprostene bunod, 0.24 mg/mL.

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)]*.

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 elsewhere in the labeling:

- Pigmentation *[see Warnings and Precautions (5.1)]*
- Eyelash Changes *[see Warnings and Precautions (5.2)]*
- Intraocular Inflammation *[see Warnings and Precautions (5.3)]*
- Macular Edema *[see Warnings and Precautions (5.4)]*
- Bacterial Keratitis *[see Warnings and Precautions (5.5)]*
- Use with Contact Lens *[see Warnings and Precautions (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 mcg/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.

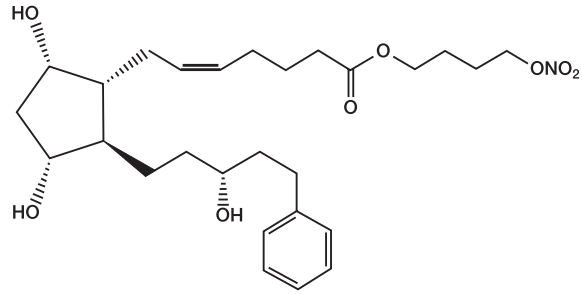
11 DESCRIPTION

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin analog formulated as a sterile topical ophthalmic solution. VYZULTA contains the active ingredient latanoprostene bunod 0.24 mg/mL, the preservative benzalkonium chloride 0.2 mg/mL, and the following inactive ingredients: polysorbate 80, glycerin, EDTA, and water. The formulation is buffered to pH 5.5 with citric acid/sodium citrate.

Its chemical name is 4-(Nitrooxy)butyl (5Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate. Its molecular formula is $C_{27}H_{41}NO_8$. Molecular weight: 507.62.

Its chemical structure is:

Figure 1



Latanoprostene bunod is a colorless to yellow oil.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Latanoprostene bunod is thought to lower intraocular pressure by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Intraocular pressure is a major modifiable risk factor for glaucoma progression. Reduction of intraocular pressure reduces risk of glaucomatous visual field loss.

12.2 Pharmacodynamics

Reduction of the intraocular pressure starts approximately 1 to 3 hours after the first administration with the maximum effect reached after 11-13 hours in eyes with elevated intraocular pressure.

12.3 Pharmacokinetics

Absorption

The systemic exposure of latanoprostene bunod and its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects after topical ocular administration of VYZULTA 0.024% once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post-dose on Day 1 and Day 28. The mean maximal plasma concentrations (Cmax) of latanoprost acid (LLOQ of 30 pg/mL) were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 minutes post-administration on both Day 1 and Day 28.

Distribution

There were no ocular distribution studies performed in humans.

Metabolism

After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety), an F2α prostaglandin analog, and butanediol mononitrate. After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Butanediol mononitrate is metabolized to 1,4-butanediol and nitric oxide. The metabolite 1,4-butanediol is further oxidized to succinic acid and enters the tricarboxylic acid (TCA) cycle.

Elimination

The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) in the majority of subjects by 15 minutes following ocular administration of VYZULTA 0.024% in humans.

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.

14 CLINICAL STUDIES

In clinical studies up to 12 months duration, patients with open-angle glaucoma or ocular hypertension with average baseline intraocular pressures (IOPs) of 26.7 mmHg, the IOP-lowering effect of VYZULTA (latanoprostene bunod ophthalmic solution) 0.024% once daily (in the evening) was up to 7 to 9 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is supplied in low density polyethylene bottles with dropper tips and turquoise caps in the following sizes:

2.5 mL fill in a 4 mL white container - NDC 24208-504-02

5 mL fill in a 7.5 mL natural container - NDC 24208-504-05

Storage: Unopened bottle should be stored refrigerated at 2° to 8°C (36° to 46°F). Once a bottle is opened it may be stored at 2° to 25°C (36° to 77°F) for 8 weeks.

During shipment, bottles may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

Protect from light. Protect from freezing.

17 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 is usually reversible after discontinuation of VYZULTA.

- *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 VYZULTA. 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*

  Advise patients that if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of VYZULTA.

- *Use with Contact Lenses*

  Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of VYZULTA.

- *Use with Other Ophthalmic Drugs*

  If more than one topical ophthalmic drug is being used, the drugs should be administered with at least five (5) minutes between applications.

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767 and 8,058,467

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