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

Initial U.S. Approval: 2017

--- CONTENTS ---
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 USE IN SPECIFIC POPULATIONS
8 CLINICAL PHARMACOLOGY
9 NONCLINICAL TOXICOLOGY
10 DESCRIPTION
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 HOW SUPPLIED/STORAGE AND HANDLING
16 PATIENT COUNSELING INFORMATION

--- HIGHLIGHTS OF PRESCRIBING INFORMATION ---

FULL PRESCRIBING INFORMATION: 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.

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--- 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 periocular 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2019

--- INTRACULAR 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.

--- 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.

--- 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 LENS ---

Contact lenses should be removed prior to the administration of VYZULTA. The product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

--- 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)]

--- 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.
Molecular weight: 507.62. Its chemical structure is:

![Chemical Structure](image)

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 F2x 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 while 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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