Product Information

**Product Trade:** VYZULTA®

**Delivery:** Topical ophthalmic solution

**Active ingredient:** Latanoprostene bunod 0.24 mg/mL

**Inactive ingredients:** Polysorbate 80, glycerin, ethylenediaminetetraacetic acid (EDTA), water, benzalkonium chloride 0.2 mg/mL (preservative), citric acid/sodium citrate (to adjust the pH to 5.5)

**How supplied:** Low density polyethylene, 7.5 (natural) or 4.0 mL (white) bottle with dropper tip and a turquoise cap

**Indication:** VYZULTA is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

**Fill size:** 2.5 mL / 5 mL

No A/B Generic Equivalent Available.

**Selling unit:**

<table>
<thead>
<tr>
<th>Fill</th>
<th>NDC</th>
<th>Dimensions</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mL</td>
<td>24208-0504-02</td>
<td>3.38” x 1.63” x 1.06”</td>
<td>18.14 gm</td>
</tr>
<tr>
<td>5 mL</td>
<td>24208-0504-05</td>
<td>3.38” x 1.63” x 1.06”</td>
<td>22.68 gm</td>
</tr>
</tbody>
</table>

**Shipping case:**

<table>
<thead>
<tr>
<th>Pack</th>
<th>Dimensions</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>13.56” x 10.19” x 7”</td>
<td>5.10 lb</td>
</tr>
<tr>
<td>144</td>
<td>13.56” x 10.19” x 7”</td>
<td>6.25 lb</td>
</tr>
</tbody>
</table>

**Bar coding:**

2.5 mL bottle bar-coded with NDC# 24208-0504-02
5 mL bottle bar-coded with NDC# 24208-0504-05

**Storage conditions:** 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. Protect from light and freezing

**Expiration:** 24 months (2.5 mL), 36 months (5 mL)

**Inner pack:** Shrink-wrapped in bundles of 12 units

**Customer Service Department**

Phone orders: 1-800-321-4576
Fax orders: 1-908-927-1926
Email orders: Pharmcs@Valeant.com

**Special terms:**

<table>
<thead>
<tr>
<th>Fill</th>
<th>NDC</th>
<th>WAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mL</td>
<td>24208-0504-02</td>
<td>$180.00</td>
</tr>
<tr>
<td>5 mL</td>
<td>24208-0504-05</td>
<td>$360.00</td>
</tr>
</tbody>
</table>

**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 Prescribing Information on following pages and visit vyzulta.com/rx.
2 DOSAGE AND ADMINISTRATION

One drop in the affected eye(s) once daily in the evening. (2)

5.2 Eyelash Changes

VYZULTA™ (latanoprostene bunod) may gradually change eyelashes and vellus hair in the treated eye. These changes appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod) may not be reversed, there is little evidence of its long-term effects. Patients who develop increased pigmentation, including permanent changes, should be examined regularly.

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

6.1 Clinical Trials Experience

The most commonly reported treatment-related adverse reactions included:

- Conjunctival hyperemia (4%)
- Eye irritation (2%)
- Eye pain (2%)
- Exophthalmos (2%)

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%).

6.2 Use with Contact Lens

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6.3 Use with Occlusion or Wound Healing Agents

Combination therapy with other topical ophthalmic agents, including agents that lower intraocular pressure, is not recommended due to the potential for additive or synergistic ocular hypotensive effects.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women. Use during pregnancy should be determined on an individual basis.

8.2 Lactation

It is not known whether latanoprostene bunod is excreted in human milk. Due to the known effects of other ophthalmic prostaglandin analogs, caution is advised when VYZULTA is administered to breast-feeding women.

8.3 Pediatric Use

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

17 PATIENT COUNSELING INFORMATION

17.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

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17.4 Suspected Adverse Reactions

If a patient or prescriber observes any adverse reactions not listed in this section, continue to report them to Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Animal toxicity was performed at 1500 mcg/kg/day (70 times the clinical dose), on a body surface area basis, assuming 100% absorption. 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, and butanediol mononitrate. After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost. Latanoprost and its metabolites latanoprost acid and butanediol mononitrate are considered to be the active ingredients of VYZULTA™ (latanoprostene bunod ophthalmic solution).

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 min post administration on both Day 1 and Day 28.

Distribution

There were no ocular circulation studies performed in humans.

Metabolism

After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety), an F2z prostaglandin analog, and butanediol mononitrate. After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dino-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 decreased below the LLOQ (30 pg/mL) in the majority of subjects by 15 min 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 micronuclear formation in the in vivo bone marrow micronuclear 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 assessed 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 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 47°F). Once a bottle is opened it may be stored at 2° to 25°C (76° 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.

Protection 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 spaced at least 15 minutes and 15 minutes between applications.


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Bausch & Lomb Incorporated

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