Get into the habit of applying your XALATAN eye drops at the same time every day

<table>
<thead>
<tr>
<th>DAY 1</th>
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<td>DAY 29</td>
<td>DAY 30</td>
<td>DAY 31</td>
<td>NEXT DR. VISIT</td>
<td>Notes:</td>
<td></td>
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</tbody>
</table>

Visit www.XALATAN.com for more information

Important Safety Information and Indication

XALATAN is not recommended in patients with a known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product.

XALATAN may slowly cause darkening of the eye color, darkening of the eyelid and eyelashes, and increased growth and thickness of eyelashes. Color changes may increase as long as XALATAN is administered, and eye color changes are likely to be permanent.

Please see Important Safety Information and Indication continued on next page and accompanying Full Prescribing Information.
How to Administer Your XALATAN Eye Drops

Follow these 5 steps to properly put in your eye drops:

1. Wash and dry your hands
2. Find a comfortable seat and tilt your head back slightly
3. Gently pull down your bottom eyelid
4. Use your other hand to hold the bottle and put the drop into the space between the lower lid and the eye (repeat steps 3 and 4 on your second eye)
5. Close your eyes and gently press on your tear ducts—the inner corners of the eyes—for 2 or 3 minutes; this stops the blinking action from draining the drops away. If you’re taking more than one eye drop medication, wait 5 minutes before using the second eye drop medication

To prevent infection or contamination of the solution, try not to allow the end of the bottle to make contact with the eye or anything else. And always remember to replace the bottle cap after applying the drops.

If you find it difficult to do this yourself, ask someone to follow these steps and administer the eye drops for you. Special devices are also available to improve administration of eye drops. Talk to your doctor or pharmacist.

Important Safety Information (continued)
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.
Contact lenses should be removed prior to the administration of XALATAN. Contact lenses can be reinserted 15 minutes following administration of XALATAN.
If more than one topical eye medication is used, the drugs should be administered at least five minutes apart.
The most common side effects for XALATAN may include blurred vision, burning and stinging, eye redness, eye itching, the feeling of something in the eye, increased darkening of eye color, irritation of the clear front surface of the eye, or cold or flu.

Indication
XALATAN® (latanoprost ophthalmic solution) is a prescription medication for the treatment of high eye pressure/intraocular pressure (IOP) in people with open-angle glaucoma or ocular hypertension.

Please see accompanying Full Prescribing Information.
XALATAN® (latanoprost ophthalmic solution) 0.005%

Initial U.S. Approval: 1996

INDICATIONS AND USAGE
XALATAN is a prostaglandin F2α analogue indicated for the reduction of elevated 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
Ophthalmic solution containing 50 mcg/mL latanoprost (0.005%). [3]

WARNINGS AND PRECAUTIONS
5.1 Pigmentation
Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation is expected to increase as long as latanoprost is administered. (4)

ADVERSE REACTIONS
Most common adverse reactions (≥4%) from clinical trials are blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, punctate keratitis, and upper respiratory tract infection/rasopharyngitis/influenza. (6)

DRUG INTERACTIONS
In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used, they should be administered at least 5 minutes apart. (7)

See 17 for PATIENT COUNSELING INFORMATION.

*Sections or subsections omitted from the full prescribing information are not listed
5.6 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 [see Patient Counseling Information (17)].

5.7 Use with Contact Lenses
Contact lenses should be removed prior to the administration of XALATAN, and may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS
The following adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the label:
• Iris pigmentation changes [see Warnings and Precautions (5.1)]
• Eyelid skin darkening [see Warnings and Precautions (5.1)]
• Eyelash changes (increased length, thickness, pigmentation, and number of lashes) [see Warnings and Precautions (5.2)]
• Intraocular inflammation (iritis/uveitis) [see Warnings and Precautions (5.3)]
• Macular edema, including cystoid macular edema [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

XALATAN was studied in three multicenter, randomized, controlled clinical trials. Patients received 50 mcg/mL XALATAN once daily or 5 mg/mL active-comparator (timolol) twice daily. The patient population studied had a mean age of 65±10 years. Seven percent of patients withdrew before the 6-month endpoint.

Table 1: Ocular Adverse Reactions and Ocular Signs/Symptoms Reported by 5-15% of Patients Receiving Latanoprost

<table>
<thead>
<tr>
<th>Symptom/Finding</th>
<th>Latanoprost (n=460)</th>
<th>Timolol (n=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign body sensation</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Stinging</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Itching</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Burning</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Increased pigmentation of the Iris</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Less than 1% of the patients treated with XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

Table 2: Adverse Reactions That Were Reported in 1-5% of Patients Receiving Latanoprost

<table>
<thead>
<tr>
<th>Ocular Events/Signs and Symptoms</th>
<th>Latanoprost (n=460)</th>
<th>Timolol (n=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive tearing</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Eyelid discomfort/pain</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dry eye</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Eye pain</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Eyelid margin crusting</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Erythema of the eyelid</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Photophobia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

The oculocutaneous signs and symptoms of blepharitis have been identified as “commonly observed” through analysis of clinical trial data.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

10 OVERDOSE
Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

If overdose with XALATAN occurs, treatment should be symptomatic.

11 DESCRIPTION
Latanoprost is a prostanoid F2 analog. Its chemical name is isopropyl-(2)-(1R,2R,3R,5S)-3,5-dihydroxy-2-(3R)-5-hydroxy-5-phenylpentyl[cyclopentyl]-5-heptenoate. Its molecular formula is C26H40O5 and its chemical structure is:

![Chemical structure of latanoprost]

Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

XALATAN (latanoprost ophthalmic solution) 0.005% is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of XALATAN contains 50 mcg of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dithionite, phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. One drop contains approximately 1.5 mcg of latanoprost.
**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**
Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

**12.2 Pharmacodynamics**
Reduction of the IOP in man starts about 3-4 hours after administration and maximum effect is reached after 8-12 hours. IOP reduction is present for at least 24 hours.

**12.3 Pharmacokinetics**

**Absorption**
Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active.

**Distribution**
The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

**Metabolism**
Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

**Excretion**
The elimination of the acid of latanoprost from human plasma is rapid (t1/2 = 17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical and intravenous dosing, respectively.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

**14 CLINICAL STUDIES**

**14.1 Elevated Baseline IOP**
Patients with mean baseline IOP of 24 – 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 – 8 mmHg reductions in IOP. This IOP reduction with XALATAN 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

**14.2 Progression of Increased Iris Pigmentation**
A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of XALATAN once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase. Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature, or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

**16 HOW SUPPLIED/STORAGE AND HANDLING**
XALATAN is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 mcg/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle: NDC 0013-8303-04

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to the patient, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.

**17 PATIENT COUNSELING INFORMATION**

**Potential for Pigmentation**
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XALATAN [see Warnings and Precautions (5.1)].

**Potential for Eyelash Changes**
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN. 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**
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions [see Warnings and Precautions (5.6)].

**When to Seek Physician Advice**
Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection) or 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 the multiple-dose container.

**Use with Contact Lenses**
Advise patients that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of XALATAN.

**Use with Other Ophthalmic Drugs**
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

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