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**Clinical Pharmacology**

Latanoprost is a synthetic analog of prostaglandin F₂α that is produced in the prostaglandin biosynthesis pathway. It acts as a potent agonist of the prostaglandin F₂α receptor, leading to increased uveal outflow and reduced intraocular pressure.

**Pharmacokinetics**

The systemic absorption of latanoprost ophthalmic solution is low, with bioavailability estimated to be less than 1%. The drug is rapidly absorbed through the conjunctival and lacrimal route, leading to systemic absorption. The peak plasma concentration is reached within 2-3 hours after administration.

**WARNINGS**

There have been reports of adverse reactions, including conjunctival hyperemia, eye irritation, and increased lacrimation. These reactions are common with topical ophthalmic medications and are usually mild and transient. In cases of severe conjunctival hyperemia or severe eye irritation, the medication should be discontinued and the condition assessed by a healthcare professional.

**ADVERSE REACTIONS**

Latanoprost ophthalmic solution may cause adverse reactions, such as conjunctival hyperemia, eye irritation, and increased lacrimation. These reactions are common with topical ophthalmic medications and are usually mild and transient.

**DOSAGE AND ADMINISTRATION**

Latanoprost ophthalmic solution is supplied as a solution intended for topical ophthalmic administration. The recommended dosage is one drop per affected eye once daily. The drop should be administered at bedtime or at bedtime and 12 hours later, if preferred. The dropper should be replaced in its protective cap after use to avoid contamination.

**STORAGE AND HANDLING**

Latanoprost ophthalmic solution should be stored at room temperature and protected from light. The dropper should be replaced in its protective cap after use to avoid contamination.

**COMPATIBILITY**

Latanoprost ophthalmic solution is not compatible with contact lenses. The patient should remove contact lenses before administration and not wear contact lenses for at least 15 minutes following administration of the medication.
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ADVERSE REACTIONS

Clinical Practice:
During the initial 4 days of treatment, all patients should be instructed not to use any other ocular hypotensive, antiglaucoma, or anti-inflammatory medications, including topical corticosteroids. After the initial 4 days, the use of other ocular medications may be added to the regimen.

Trials involving bevacizumab,
a monoclonal antibody directed against vascular endothelial growth factor (VEGF) in Uveal Melanoma, have been established.

CURRENT RECOMMENDATIONS
Latanoprost is generally well tolerated, and the most commonly reported side effects are blurred vision, burning, stinging, itching, redness, irritation, and an occasional change in color of the eyelashes.

In patients with ocular hypertension or open-angle glaucoma, the incidence of discontinuation due to adverse events was approximately 1% of patients

The dose of bevacizumab administered was 2 mg or 4 mg Q4W or Q8W, depending on the patient's baseline IOP.

Other adverse reactions may be similar to those reported in other anti-glaucoma or anti-inflammatory medications.

Unfortunately, no data have been established regarding the use of bevacizumab in other surgical procedures, other than uveal melanoma.

The study was performed in patients with metastatic uveal melanoma treated with a systemic combination of bevacizumab and ipilimumab.

The incidence of adverse events was similar across all treatment groups, with the most common being grade 1 or 2 and being reported in 10% of patients treated with bevacizumab alone and 4% of patients treated with the combination.

The incidence of adverse events was higher in patients treated with the combination of bevacizumab and ipilimumab compared to those treated with bevacizumab alone.
Latanoprost ophthalmic solution

0.005% (50 µg/mL)

**DESCRIPTION**
Latanoprost is a prostaglandin F₂α analogue. Its chemical name is isopropyl-(2Z)-7-[1(R,2R,3S,5S,5'-dihydroxy-2'-5'-hexylpentyl)-2'-5'-hexylpentyl]-5'-hexylpentane. Its molecular formula is C₉₄H₆₂O₂ and its chemical structure is:

![Chemical Structure of Latanoprost](image)

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

Latanoprost Sterile Ophthalmic Solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsm/kg. Each mL of latanoprost ophthalmic solution contains 50 micrograms of latanoprost, benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide phophate anhydrous and water for injection. One drop contains approximately 1.5 µg of latanoprost.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**
Latanoprost is a prostaglandin F₂α 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.

**Pharmacokinetics/Pharmacodynamics**
Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydroyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

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.

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-dihydroxy and 1,2,3,4-tetrahydro metabolites via fatty acid β-oxidation.

Excretion: The elimination of the acid of latanoprost from human plasma is rapid (T½ = 17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are renally eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

**Animal Studies**
In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris, with no proliferative changes observed. The change in iris color may be permanent.

Ocular administration of latanoprost at a dose of 6 µg/eye/day (4 times the human daily dose) to cynomolgus monkeys has also been shown to increase paltedepal pigment tissue. This effect was reversible upon discontinuation of the drug.

**INDICATIONS AND USAGE**
Latanoprost ophthalmic solution is indicated for the treatment of increased intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

**WARNINGS**
Latanoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, perilobular tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as latanoprost ophthalmic solution is administered.

After discontinuation of latanoprost ophthalmic solution, pigmentation of the iris is likely to be permanent while pigmentation of the perilobular tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

**PRECAUTIONS**
Latanoprost ophthalmic solution may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see WARNINGS). 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 recoll or bleaching of the iris appear to be affected by treatment. While treatment with latanoprost ophthalmic solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

**EYELID SKIN DARKENING**
Latanoprost ophthalmic solution may be associated with eyelash and/or eyelid changes in the treated eye during treatment with latanoprost ophthalmic solution. These changes may occur in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or eyelid hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Latanoprost ophthalmic solution 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.

**MACULAR EDEMA**
Latanoprost ophthalmic solution contains benzalkonium chloride, a surfactant. The potential ocular toxicity of benzalkonium chloride is unknown. It is not known whether benzalkonium chloride is absorbed systemically from the eye. The potential adverse effects of benzalkonium chloride on the ocular surface and the systemic effects should be considered when evaluating the benefit of treatment with latanoprost ophthalmic solution.

**Drug Interactions**
In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution. If such drugs are used they should be administered at least five minutes apart.

**PRECAUTIONS, Information for Patients**
Latanoprost ophthalmic solution may be associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent upper respiratory infection or a disruption of the ocular epithelial surface (see PRECAUTIONS, Information for Patients).

**Contact Lenses**
Contact lenses should be removed prior to the administration of latanoprost ophthalmic solution, and may be reinstituted 15 minutes after administration (see PRECAUTIONS, Information for Patients).

**Information for Patients**
Latanoprost ophthalmic solution may be associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent upper respiratory infection or a disruption of the ocular epithelial surface (see PRECAUTIONS, Information for Patients).

**PRECAUTIONS**
Latanoprost ophthalmic solution may be associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent upper respiratory infection or a disruption of the ocular epithelial surface (see PRECAUTIONS, Information for Patients).
**latanoprost ophthalmic solution**

or female fertility in animal studies.

**Pregnancy:** Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 18 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose.

There are no adequate and well-controlled studies in pregnant women. Latanoprost ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when latanoprost ophthalmic solution is administered to a nursing woman.

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

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

**ADVERSE REACTIONS**

Adverse events referred to in other sections of this insert:

Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and mucosal edema, including cystoid macular edema (see WARNINGS and PRECAUTIONS).

Controlled Clinical Trials:

- The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on latanoprost ophthalmic solution in the three 6-month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy.

- Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with latanoprost ophthalmic solution required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1 to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia.

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

**latanoprost ophthalmic solution**

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with latanoprost ophthalmic solution were upper respiratory tract infection/cold/flul, which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

**Clinical Practice:**

The following events have been identified during postmarketing use of latanoprost ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost ophthalmic solution, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; dizziness, headache, and toxic epidermal necrolysis.

**OVERDOSAGE**

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of large doses of latanoprost in monkeys has been associated with transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with latanoprost, bronchoconstriction was not induced. Intravenous infusion of up to 3 μg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

If overdosage with latanoprost ophthalmic solution occurs, treatment should be symptomatic.

**DOSAGE AND ADMINISTRATION**

The recommended dosage is one drop (1.5 μg) in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose as normal.

The dosage of latanoprost ophthalmic solution should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including latanoprost ophthalmic solution is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure lowering effect or cause paradoxical elevations in IOP.

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

Latanoprost ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

**HOW SUPPLIED**

Latanoprost ophthalmic solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 μg/mL). It is supplied as a 2.5 mL solution in a 5 mL Clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

**2.5 mL vials, 8.005% (50 μg/mL)**

Multi-Pack of 3 bottles  NDC 59762-0333-1

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.

Rx only

**GREENSTONE® BRAND**

Distributed by: Greenstone LLC

Peapack, NJ 07977

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