**Xalatan®**

**latanoprost ophthalmic solution**

0.005% (50 μg/mL)

**DESCRIPTION**

Latanoprost is a prostaglandin E₂ analogue. Its chemical name is Isopropyl-(2Z)-7(11E)-19,2R,3R,5S,5S,5, 7-dihydroxy-2,15(16)-dihydroxy-5,6-phenylbiis[5]cyclopentenyl-5,5-heptanate. Its molecular formula is C₂₂ H₃₂ O₆ and its chemical structure is:

![Chemical Structure of Latanoprost](image)

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

**XALATAN 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 XALATAN contains 50 micrograms of latanoprost, benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate 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 which is believed to reduce the intraocular pressure by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow.

**Pharmacokinetics/Pharmacodynamics**

**Absorption:** Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed 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 half-life of latanoprost could be measured in aqueous humor during the first 4 hours, and in plasma 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 diol and 1,2,3,4-tetrahydropyridine through fatty acid β-oxidation.

**Excretion:** The elimination of the acid of latanoprost from human plasma was rapid (T½ β ~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 84% and 96% 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 results from the preclinical program demonstrated that the increased pigmentation is unlikely to be associated with proliferation of melanocytes. It appears that the mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma.

In ocular toxicity studies, administration of latanoprost at a dose of 6 μg/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased papillary responses. This effect has been reversible and occurred at doses above the standard clinical dose level.

**INDICATIONS AND USAGE**

**XALATAN Sterile Ophthalmic Solution** is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive to achieve target IOP determined after multiple measurements over time to another intraocular pressure lowering medication.
CLINICAL STUDIES

Patients with mean baseline intracocular pressure of 24–25 mmHg who were treated for 6 months in multicenter, randomized, controlled trials demonstrated 6–8 mmHg reduction in intracocular pressure. The IOP reduction with XALATAN Sterile Ophthalmic Solution 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

XALATAN has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the irises and perilobular tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

XALATAN Sterile Ophthalmic Solution may gradually change eye color, increasing the amount of brown pigment in the irises by increasing the number of melanocytes pigmentation granules in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of XALATAN.

XALATAN may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

If patients are expected to receive treatment in only one eye, one should be informed about the potential for increased brown pigmentation of the iris, perilobular tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent.

PRECAUTIONS

General: Latanoprost is hydrolyzed in the cornea. The effect of continued administration of XALATAN Sterile Ophthalmic Solution on the corneal endothelium has not been fully evaluated.

There have been reports of bacterial keratitis 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 corneal disease or a disruption of the ocular epithelial surface. See Information (for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see WARNINGS). Typically the brown pigmentation occurs around the pupil and horizontally towards the periphery. In affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. During clinical trials, the increase in brown iris color has not been shown to progress further upon discontinuation of treatment. But the number of patients to be followed for longer than 1 year has been limited. Color change may be permanent. Neither new nor freckles of the iris have been affected by treatment.

XALATAN should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Neuropathy. Intraocular refractive surgery (IOLs) has been reported during treatment with XALATAN. These reports have mainly occurred in astigmatic patients. In pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for retinal edema, XALATAN should be used with caution in these patients.

There is limited experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma.

XALATAN has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

XALATAN should not be administered while wearing contact lenses.

Information for Patients (see WARNINGS): Patients should be informed about the possibility of iris color change due to an increase in the brown pigment and resultant cosmetically different eye coloration that may occur when only one eye is treated. Iris pigmentation changes may be more noticeable in patients with green brown, blue grey, brown or yellow brown irides.

Patients should also be informed of the possibility of eyelash changes in the treated eye, which may result in a disparity between eyes in length, thickness, pigmentation, and number.

Patients should also be informed about the possibility of eyelid skin darkening.

The increased pigmentation to the lids and eyelid, as well as the changes to the eyelashes, may be permanent.

Patients should be instructed 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.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, infection or have ocular surgery), they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that XALATAN contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of XALATAN.

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

Drug Interaction: 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 with an interval of at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Latanoprost was not mutagenic in bacteria. In mouse lymphoma or in mouse micronucleus tests.

Chromosome aberrations were observed in vitro with human lymphocytes.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2,800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.
Xalatan
brand of latanoprost ophthalmic solution

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.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 90 times the maximum human dose, and the highest nonteratogenic dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether the drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XALATAN 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 (Iris/uvettes); iris pigmentation changes; and macular 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 XALATAN Sterile Ophthalmic Solution in the 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 lid, punctate epithelial keratopathy.

Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with XALATAN 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.

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 XALATAN were upper respiratory tract infection/cold/flu, 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 XALATAN 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 XALATAN, or a combination of these factors, include: asthma and exacerbation of asthma, corneal edema and erosions, dyspnea, eyelash changes, increased length, thickness, pigmentation, and number of lashes; eyelid skin darkening; herpes keratitis; intraocular inflammation (iris/uveitis); keratitis; macular edema, including cystoid macular edema; and toxic epidermal necrolysis.

OVERDOSAGE
Apart from ocular irritation and conjunctival or epithelial 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 5 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 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flashes, nausea and sweating. If overdose with XALATAN Sterile Ophthalmic Solution occurs, treatment should be symptomatic.

and vellus hair misplaced eyelashes sometimes resulting in eye irritation;
DOSAGE AND ADMINISTRATION

The recommended dosage is one drop (1.5 µg) in the affected eye(s) once daily in the
evening.

The dosage of XALATAN Sterile Ophthalmic Solution should not exceed once daily since
it has been shown that more frequent administration may decrease the intraocular pres-
sure lowering effect.

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

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

NOW SUPPLIED

XALATAN Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless
solution of latanoprost 0.005% (50 µg/mL) in a single plastic ophthalmic dispenser bot-
tle with a dropper tip and tamper evident overcap.

NDC 0015-8505-04
2.5 mL, 0.005% (50 µg/mL)

Storage: Protect from light. Store unopened bottle under refrigeration at 2°C to 8°C (36°F
to 46°F).

Once opened the 2.5 mL container may be stored at room temperature up to 25°C (77°F)
for 6 weeks.

Rx only

U.S. Patent Nos. 5,399,353; 5,266,504 and 5,422,868

Manufactured for:
Pharma & Upjohn Company
Kalamazoo, MI 49001, USA

By:
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098, USA

Revised November 2000

It is supplied as a 2.5 mL solution in a 5 mL clear
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.
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/s/

Wiley Chambers
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