LATANOPROST- latanoprost solution/ drops
NuCare Pharmaceuticals,Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LATANOPROST OPHTHALMIC SOLUTION safely and effectively. See full prescribing information for LATANOPROST OPHTHALMIC SOLUTION.

LATANOPROST ophthalmic solution 0.005%

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Latanoprost is a prostaglandin $F_{2}\alpha$ 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)

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product. (4)

WARNINGS AND PRECAUTIONS

- Pigmentation: pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation likely to be permanent. (5.1)
- Eyelash Changes: gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

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 epithelial keratopathy, and upper respiratory tract infection/cold/flu. (6).
To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with Latanoprost. If such drugs are used, they should be administered at least 5 minutes apart. (7)
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Latanoprost Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop 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 is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure (IOP) lowering effect or cause paradoxical elevations in IOP.

Reduction of the IOP 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 IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. Contact lenses should be removed prior to the administration of latanoprost ophthalmic solution, and may be reinserted 15 minutes after administration.

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic solution containing 50 mcg/mL latanoprost.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

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

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital 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. Beyond 5 years the effects of increased pigmentation are not known [*see Clinical Studies (14.2*)].

Iris color change may not be noticeable for several months to years. 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 nevi nor freckles of the iris appear to be affected by treatment. While treatment with latanoprost can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [*see Patient Counseling Information (17.1)*].

5.2 Eyelash Changes

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or

hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment [*see Patient Counseling Information (17.2)*].

5.3 Intraocular Inflammation

Latanoprost 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 because inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Latanoprost ophthalmic solution 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.

5.5 Herpetic Keratitis

Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost ophthalmic solution. Latanoprost should be used with caution in patients with a history of herpetic keratitis. Latanoprost should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

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 (17.3)*].

5.7 Use with Contact Lenses

Contact lenses should be removed prior to the administration of latanoprost ophthalmic solution, 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.

Latanoprost was studied in three multicenter, randomized, controlled clinical trials. Patients received 50 mcg/mL latanoprost 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

Symptom/Finding	**Adverse Reactions (incidence (%))**	
	Latanoprost (n=460)	**Timolol (n=369)**
Foreign body sensation	13	8
Punctate epithelial keratopathy	10	9
Stinging	9	12
Conjunctival hyperemia	8	3
Blurred vision	8	8
Itching	8	8
Burning	7	8
Increased pigmentation of the iris	7	0

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

Table 2: Adverse Reactions that were reported in 1–5% of patients receiving Latanoprost

	Adverse Reactions (incidence (%))	
	Latanoprost (n=460)	**Timolol (n=369)**
Ocular Events/Signs and Symptoms		
Excessive tearing	4	6
Lid discomfort/pain	4	2
Dry eye	3	3
Eye pain	3	3
Lid crusting	3	3
Lid erythema	3	2
Photophobia	2	1
Lid edema	1	3

Systemic Events		
Upper respiratory tract infection/cold/flu	3	3
Muscle/joint/back pain	1	0.5
Rash/allergic skin reaction	1	0.3

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of latanoprost in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost, or a combination of these factors, include:

Nervous System disorders: dizziness, headache, and toxic epidermal necrolysis

Eye Disorders: eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; periorbital and lid changes resulting in deepening of the eyelid sulcus.

Respiratory, Thoracic and Mediastinal Disorders: asthma and exacerbation of asthma; dyspnea

Skin and Subcutaneous Tissue Disorders: eyelid skin darkening

Infections and Infestations: Herpes keratitis

7 DRUG INTERACTIONS

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 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 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 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 is administered to a nursing woman.

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 OVERDOSAGE

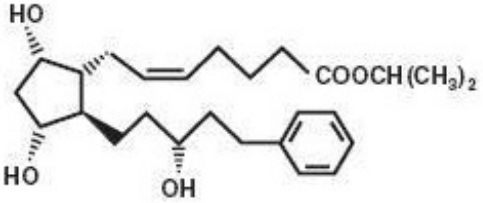
Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

If overdosage with latanoprost occurs, treatment should be symptomatic.

11 DESCRIPTION

Latanoprost is a prostaglandin $F_{2}\alpha$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_{5}$ and its chemical structure is:

M.W. 432.58



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.

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 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, 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 ($t_{1/2}$ = 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 latanoprost 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 latanoprost 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

Latanoprost ophthalmic solution 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 4 mL clear low density polyethylene bottle with a low density polyethylene dropper tip, and a turquoise high density polypropylene screw cap, and a clear PVC film with a single perforation.

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle:

NDC 68071-4612-2

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

17.1 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 Latanoprost ophthalmic solution [*see Warnings and Precautions (5.1)*].

17.2 Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with Latanoprost ophthalmic solution. 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.

17.3 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)*].

17.4 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.

17.5 Use with Contact Lenses

Advise patients that Latanoprost ophthalmic solution 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 Latanoprost ophthalmic solution.

17.6 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.

Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

Revised: June 2016

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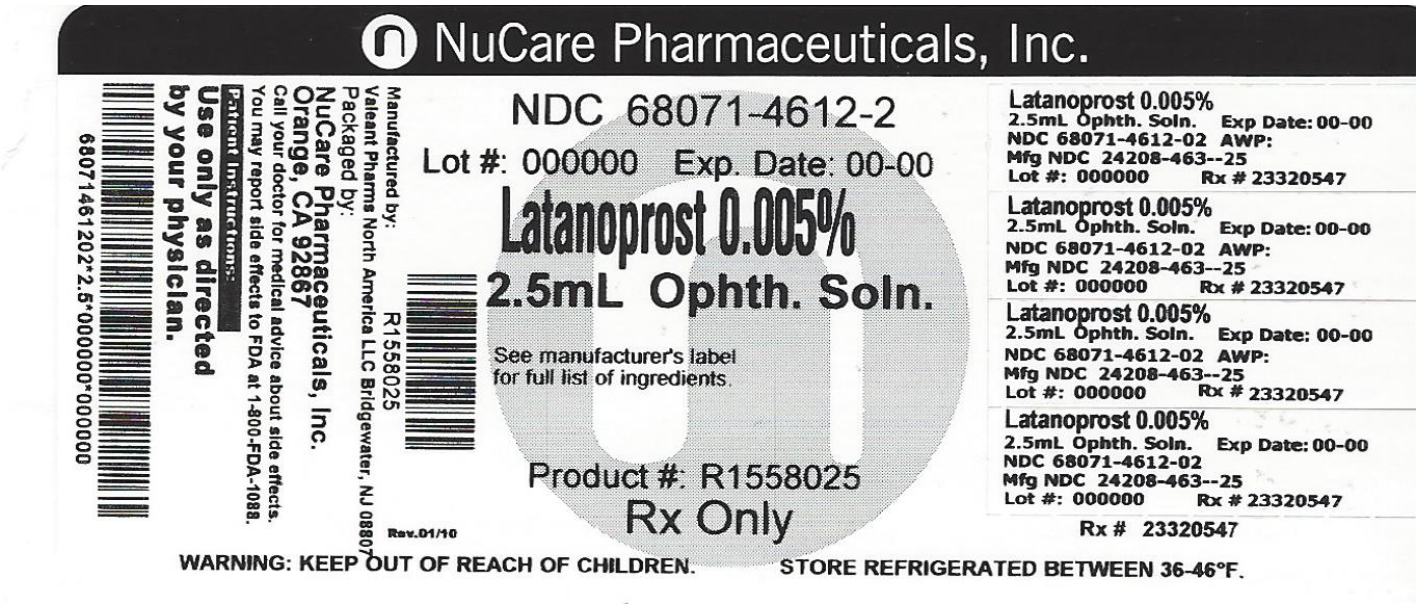
PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



LATANOPROST

latanoprost solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68071-4612(NDC:24208-463)
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LATANOPROST (UNII: 6Z5B6HVF6O) (LATANOPROST - UNII:6Z5B6HVF6O)	LATANOPROST	50 ug in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	
SODIUM PHOSPHATE, MONOBASIC, UNSPECIFIED FORM (UNII: 3980JIH2SW)	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68071-4612-2	2.5 mL in 1 BOTTLE; Type 0: Not a Combination Product	10/23/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201006	03/22/2011	

Labeler - NuCare Pharmaceuticals,Inc. (010632300)

Establishment

Name	Address	ID/FEI	Business Operations
NuCare Pharmaceuticals,Inc.		010632300	relabel(68071-4612)

Revised: 2/2022 NuCare Pharmaceuticals,Inc.