9 PM Eye Drops (Latanoprost 0.005%)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Qualitative and Quantitative Composition

Each ml contains:
Latanoprost IP..... 50 mcg
Benzalkonium Chloride, IP ..... 0.02% w/v

(as preservative)
Isotonic aqueous vehicle ..... q.s.

Dosage Form and Strength

Ophthalmic solution of Latanoprost 50 mcg

Clinical Particulars

Therapeutic Indications

9 PM ophthalmic solution is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension.

Posology and Method of Administration

Adults (including the elderly)

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 **9 PM** ophthalmic solution should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogues 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.

Reduction of IOP starts approximately 3–4 hours after administration and the maximum effect is reached after 8–12 hours.

Latanoprost 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 5 minutes apart. Contact lenses should be removed prior to the administration of **9 PM** ophthalmic solution, and may be reinserted 15 minutes after administration.

Contraindications

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

product.

Special Warnings and Precautions for Use

Pigmentation

Latanoprost ophthalmic solution 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, and growth of eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the stromal melanocytes of the iris 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. The effects of increased pigmentation beyond five years are not known. Unilateral treatment can result in permanent heterochromia.

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.

This change in eye color has predominantly been seen in patients with mixed colored irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the onset of the change is usually within the first eight months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation. The iris color change is slight in majority of cases and often not observed clinically. The incidence in patients with mixed color irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

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. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on five years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and Latanoprost ophthalmic solution can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, Latanoprost ophthalmic solution treatment may be discontinued.

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.

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.

Macular edema

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

There is limited experience with Latanoprost ophthalmic solution in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of Latanoprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Latanoprost has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that Latanoprost ophthalmic solution should be used with caution in these conditions until more experience is obtained.

Peri-operative Period of Cataract Surgery

There are limited study data on the use of Latanoprost during the peri-operative period of cataract surgery. Latanoprost should be used with caution in these patients.

Herpetic Keratitis

Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin.

Asthma

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnea were reported in post-marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience.

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.

Preservative

9 PM ophthalmic solution contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye

patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Use with Contact Lenses

Contact lenses may absorb benzalkonium chloride and these should be removed before applying **9 PM** ophthalmic solution but may be reinserted after 15 minutes.

Drug Interactions

Definitive drug interaction data are not available.

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 with an interval of at least five minutes between instillations.

The combined use of two or more prostaglandins, or prostaglandin analogues 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.

Use in Special Population

Pregnant Women

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 non-embryocidal dose in rabbits was approximately 15 times the maximum human dose.

There are no adequate and well-controlled studies in pregnant women. Latanoprost 0.005% ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactating Women

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.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients

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

Effects on Ability to Drive and Use Machines

Latanoprost ophthalmic solution has minor influence on the ability to drive and use machines. In

common with other eye preparations, instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

Undesirable Effects

The following adverse reactions were reported in post-marketing experience and are discussed in greater detail in other sections of the label:

- Iris pigmentation changes [*see Warnings and Precautions*]
- Eyelid skin darkening [*see Warnings and Precautions*]
- Eyelash changes (increased length, thickness, pigmentation, and number of lashes)
- Intraocular inflammation (iritis/uveitis) [*see Warnings and Precautions)*]
- Macular edema, including cystoid macular edema [*see Warnings and Precautions*]

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 0.005% ophthalmic solution was studied in three multi-center, 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

	Adverse Reactions (incidence (%)	
Symptom/Finding	**Latanoprost (n=460)**	**Timolol (n=369)**
Foreign body sensation	13	8
Punctate keratitis	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 0.005% ophthalmic solution 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 (%)	
Ocular events/ Signs & Symptoms	**Latanoprost (n=460)**	**Timolol (n=369)**
Excessive tearing	4	6

Eyelid discomfort/ pain	4	2
Dry eye	3	3
Eye pain	3	3
Eyelid margin crusting	3	3
Erythema of the eyelid	3	2
Photophobia	2	1
Eyelid Edema	1	3
Systemic events		
Upper respiratory tract infection/nasopharyngitis/influenza	3	3
Myalgia/arthralgia/back pain	1	0.5
Rash/allergic skin reaction	1	0.3

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

Summary of the Safety Profile

The majority of adverse reactions relate to the ocular system. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation. Other ocular adverse reactions are generally transient and occur on dose administration.

Tabulated list of adverse events

Adverse events are categorized by frequency as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to < 1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**
Infections and infestations				Herpetic keratitis*§	
Nervous system disorders			Headache*; dizziness*		

Eye disorders	Iris hyperpigmentation; mild to moderate conjunctival hyperemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes)	Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis*	Eyelid edema; dry eye; keratitis*; vision blurred; macular edema including cystoid macular edema*; uveitis*	Iritis*; corneal edema*; corneal erosion; periorbital edema; trichiasis*; distichiasis; iris cyst*§; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva*§	Periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders			Angina; palpitations*		Angina unstable
Respiratory, thoracic and mediastinal disorders			Asthma*; dyspnea*	Asthma exacerbation	
Skin and subcutaneous tissue disorders			Rash	Pruritus	
Musculoskeletal and connective tissue disorders			Myalgia*; arthralgia*		
General disorders and administration site conditions			Chest pain*		

*ADR identified post-marketing

§ADR frequency estimated using “The Rule of 3”

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Pediatric Population

In two short-term clinical trials (≤ 12 weeks), involving 93 (25 and 68) pediatric patients the safety profile was similar to that in adults and no new adverse events were identified. The short-term safety profiles in the different pediatric subsets were also similar. Adverse events seen more frequently in the pediatric population as compared to adults are: nasopharyngitis and pyrexia.

Post-marketing Experience

The following events have been identified during post-marketing use of Latanoprost 0.005% in clinical practice. Because they are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug

exposure. 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; toxic epidermal necrolysis

Eye Disorders: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; trichiasis; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst; eyelid skin darkening; localised skin reaction on the eyelids; conjunctivitis; pseudopemphigoid of the ocular conjunctiva

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

Skin and Subcutaneous Tissue Disorders: Pruritus

Infections and Infestations: Herpes keratitis

Cardiac Disorders: Angina; palpitations; angina unstable

General Disorders and Administration Site Conditions: Chest pain

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.

If Latanoprost ophthalmic solution is accidentally ingested, the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolized during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5–10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of Latanoprost.

If overdosage with latanoprost occurs, treatment should be symptomatic.

Pharmacological Properties

Mechanism of Action

Latanoprost is a prostaglandin F_2 (alpha) analogue. Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the IOP by increasing the outflow of the aqueous humour. Studies in animals and humans 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.

Pharmacodynamic properties

Reduction of the IOP in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. IOP reduction is maintained for at least 24 hours.

Pivotal studies have demonstrated that Latanoprost is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperemia may occur during topical treatment.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment. Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.

Clinical studies

Elevated Baseline IOP

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

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 0.005% ophthalmic solution 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 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.

Pediatric population

The efficacy of Latanoprost 0.005% ophthalmic solution in pediatric patients ≤ 18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma.

Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 50 mcg/mL once daily or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in IOP from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to <3 years, 3 to < 12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 to < 3 years were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 to < 1 year old in the clinical pediatric study.

No data are available for preterm infants (less than 36 weeks gestational age). IOP reductions among subjects in the primary congenital glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup. The effect on IOP was seen after the first week of treatment (see table) and was maintained throughout the 12-week period of study, as in adults.

Table 3: IOP reduction (mmHg) at week 12 by active treatment group and baseline diagnosis

	Latanoprost N=53		Timolol N=54	
Baseline Mean (SE)	27.3 (0.75)		27.8 (0.84)	
Week 12 Change from Baseline Mean[†](SE)	-7.18 (0.81)		-5.72 (0.81)	
p-value vs. timolol	0.2056			
	PCG N=28	Non-PCG N=25	PCG N=26	Non-PCG N=28
Baseline Mean (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12 Change from Baseline Mean[†](SE)	-5.90 (0.98)	-8.66 (1.25)	-5.34 (1.02)	-6.02 (1.18)
p-value vs. timolol	0.6957	0.1317		

SE: standard error.

†Adjusted estimate based on an analysis of covariance (ANCOVA) model.

Pharmacokinetic Properties

Absorption

Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolysed to the acid form to become biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in

the aqueous humour 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 humour is reached about two hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of the drug reach the posterior segment.

Metabolism

Latanoprost, an isopropyl ester prodrug, is hydrolysed 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 (beta)-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid ($t_{½}$ = 17 minutes) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic (beta)-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Pediatric Population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 pediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 mcg/mL, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to < 12 year olds and 6-fold higher in children < 3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained. Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (< 20 minutes), similar for pediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

Non-Clinical Properties

Animal Toxicology or Pharmacology

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.

Pre-clinical Safety Data

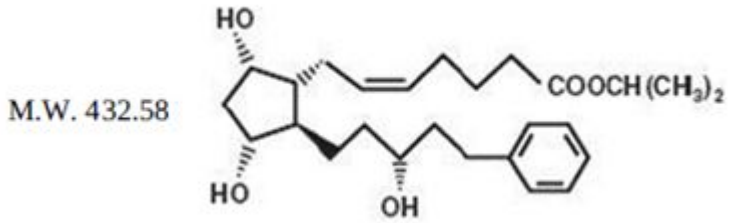
The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1,000 times. High doses of latanoprost, approximately 100 times the

clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration.

In animal studies, latanoprost has not been found to have sensitising properties. In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, 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 colour may be permanent. In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

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:



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.

Pharmaceutical Particulars

Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost ophthalmic solution. If such medicinal products are used, the eye drops should be administered with an interval of at least five minutes between instillations.

Shelf-life

As on the pack.

Packaging Information

9 PM Eye Drops: Vial of 2.5 ml

Storage and Handling Instructions

Protect from light. Store unopened bottle(s) under refrigeration at 2–8°C (36–46°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.

Patient Counselling Information

Potential for Pigmentation

Advise patients that there is a 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.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash changes and vellus hair changes in the treated eye during the treatment with latanoprost. 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 eyes or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eyes and subsequent loss of vision may result from using contaminated solutions.

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 multi-dose container.

Use with Contact Lenses

Advise patients that **9 PM** ophthalmic solution contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the ophthalmic solution, but may be reinserted 15 minutes after administration **9 PM** eye drops.

Use with Other Ophthalmic Drugs

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

Details of Manufacturer

Manufactured by CIPLA LTD.

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Ganpatrao Kadam Marg

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