PRODUCT MONOGRAPH

^{Pr}LATANOPROST

(Latanoprost Ophthalmic Solution)
50 µg/mL

Prostaglandin $F_{2\alpha}$ analogue

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ACTION AND CLINICAL PHARMACOLOGY

LATANOPROST (latanoprost), a prostaglandin $F_{2\alpha}$ (13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ isopropyl ester) analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow.

Glaucoma is a disease with characteristic optic nerve damage and a corresponding visual field defect. Increased intraocular pressure (IOP) is one of the main risk factors. However, disturbances in blood flow may also play a role in some cases. In ocular hypertension, patients may have increased IOP but without changes in the visual field or corresponding optic nerve damage.

Latanoprost is a sterile, isotonic, buffered aqueous solution with a pH of approximately 6.7.

Each mL contains 50 µg of latanoprost, a colourless to slightly yellow oil. Latanoprost is an isopropyl ester prodrug which is well absorbed through the cornea and upon entering the aqueous humour is rapidly and completely hydrolysed to the biologically active acid. Studies in humans indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration.

Following topical administration in monkeys, latanoprost is primarily distributed in the anterior segment, conjunctiva and eyelids with only minute quantities reaching the posterior segment.

Reduction of IOP following a single dose in humans starts about 3 to 4 hours following topical administration, and the maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

There is practically no metabolism of the acid of latanoprost in the eye. The plasma clearance is rapid and occurs in the liver. In humans, the half-life of the biologically active acid in plasma is approximately 17 minutes. In animal studies, the main metabolites were the 1,2-dinor and the 1,2,3,4-tetranor metabolites which exerted only weak or no biologic activity, and were excreted primarily in urine.

Clinical Studies

In five controlled clinical trials of up to 6 months duration, reduction of IOP was evaluated in patients with open-angle glaucoma or ocular hypertension treated with either latanoprost dosed once a day or timolol dosed twice a day. The mean baseline IOP (mmHg) in these studies ranged from 23.1 to 29.9 and 23.1 to 28.7 for the groups treated with latanoprost and timolol, respectively. The results are shown below.

Reduction of IOP (mmHg) in Patients Treated with Latanoprost as Compared to Timolol*

Study (ref. #)	No. of Patients		Baseline IOP mmHg		Change from Baseline mmHg (%)**		Between Group Comparison (p-Value)
	Latanoprost	Timolol	Latanoprost	Timolol	Latanoprost	Timolol	
Study 1 (24)	128	140	24.4	24.1	-6.2 (25.4)	-4.5 (17.8)	<0.001
Study 2 (26)	149	145	25.2	25.4	-7.9 (30.9)	-7.4 (29.1)	0.2
Study 3 (2)	183	84	25.1	24.6	-7.8 (30.7)	-6.6 (26.0)	0.002
Study 4 (34)	30	30	29.9	28.7	-11.7 (39.1)	-8.5 (29.6)	0.045
Study 5 (35)	76	78	23.1	23.1	-6.2 (26.8)	-4.4 (19.0)	<0.001

* Intent-to-treat (ITT) analysis, except for Study 5, which evaluated data for patients who completed the study
** Mean diurnal IOPs (mean of 3 different daytime readings) used in Studies 1-4. Mean morning IOPs, representing trough values for both treatments, used in Study 5.

In latanoprost studies of up to 24 months duration, there was no evidence of long-term drift in IOP reduction; the mean diurnal IOP reduction remained constant in patients treated up to 24 months.

Similar results were obtained from a 3 month phase III clinical trial in Asian patients with chronic angle closure glaucoma. In this study, 137 patients received latanoprost once daily and 138 patients received timolol twice daily. Latanoprost reduced IOP by 30% from the untreated baseline of 25.2 mmHg. Timolol reduced IOP by 20% from a baseline of 25.9 mmHg. The p-value for the difference between the IOP reduction by latanoprost versus timolol was $p<0.001$. The benefit to patients from latanoprost was irrespective of their degree of angle closure.

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. In the study, IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

Clinical trials have shown that latanoprost has no significant effect on production of aqueous humour and no effect on the blood-aqueous barrier. At clinical dose levels, latanoprost has negligible or no effects on intraocular blood circulation when studied in monkeys. However, mild to moderate conjunctival or episcleral hyperemia may occur as a result of topical administration.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short term treatment.

Phase II clinical trials have also demonstrated that latanoprost is effective in combination with other drugs used for treatment of glaucoma. The IOP reducing effect of latanoprost is additive to that of beta-adrenergic antagonists (timolol), adrenergic agonists (dipivefrin, epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide).

INDICATIONS AND CLINICAL USE

LATANOPROST (latanoprost) is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. LATANOPROST may be used for the reduction of intraocular pressure in patients with chronic angle-closure glaucoma who underwent peripheral iridotomy or laser iridoplasty.

See information in sections of **ACTION AND CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS** AND **ADVERSE REACTIONS.**

CONTRAINDICATIONS

Known hypersensitivity to benzalkonium chloride or any other ingredient in this product.

WARNINGS

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, and growth of eyelashes. Pigmentation is expected to increase as long as latanoprost is administered. 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 5 years are not known.** Patients who are expected to receive treatment in only one eye should be informed about the potential for increased pigmentation in the treatment eye and thus, heterochromia between the eyes.

Fertililty

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

Use in Pregnancy

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 (see TOXICOLOGY). Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

The active substance in latanoprost ophthalmic solution and its metabolites may pass into breast milk and latanoprost should therefore be used with caution in nursing women (see TOXICOLOGY).

Use in Pediatrics

The safety and efficacy of the use of latanoprost in children has not been established.

PRECAUTIONS

General

Latanoprost may gradually increase the pigmentation of the iris. This effect has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, green-brown or yellow-brown. The eye colour change is due to increased melanin content in the stromal melanocytes 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 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 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 colour change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost (see **WARNINGS).**

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.

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule, or in patients with known risk factors for macular edema. Latanoprost should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is no experience with latanoprost in patients with inflammatory ocular conditions, inflammatory glaucoma, neovascular glaucoma or congenital glaucoma, and only limited experience with pseudophakic patients and in patients with pigmentary glaucoma.

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.

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 and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

There is no experience in patients with severe or uncontrolled asthma. Such patients should therefore be treated with caution until there is sufficient experience (see ADVERSE REACTIONS AND PHARMACOLOGY, HUMAN PHARMACODYNAMICS for experience in patients with mild to moderate asthma).

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

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 ocular epithelial surface (see INFORMATION FOR THE CONSUMER).

Contact lenses should be removed prior to the administration of latanoprost, and may be reinserted 15 minutes after administration (see INFORMATION FOR THE CONSUMER).

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 with an interval of at least 5 minutes between applications.

ADVERSE REACTIONS

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

Local conjunctival hyperemia was observed: however, less than 1% of the latanoprost treated patients 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 edema, lid erythema, lid discomfort/pain 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 latanoprost were upper respiratory tract infection/cold/flu which occurred at a rate of approximately 4%. Pain in muscle/joint/back, chest pain/angina pectoris and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with

a torn posterior lens capsule, or in patients with known risk factors for macular edema. Latanoprost should be used with caution in these patients. Upon discontinuation of latanoprost treatment, visual acuity has improved, in some cases with concurrent treatment with topical steroidal and non-steroidal anti-inflammatory drugs.

Latanoprost has been reported to cause darkening, thickening and lengthening of eye lashes.

Based on spontaneous reports, rare cases of iritis/uveitis and very rare cases of darkening of the palpebral skin have been reported.

The following events, 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, have been reported during postmarketing use of latanoprost in clinical practice and in the literature: eyelash changes (increased length, thickness, pigmentation of eyelashes, increased number of eyelashes and vellus hairs on the eyelid, curling of eyelashes, misdirected eyelashes sometimes resulting in eye irritation); eyelid skin darkening: periorbital and lid changes resulting in deepening of the eyelid sulcus; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; corneal edema and erosions; localized skin reaction on the eyelid; photophobia; toxic epidermal necrolysis; infections and infestations: herpetic keratitis. Those events are reported voluntarily from a population of unknown size; therefore, estimates of frequency cannot be made. Rare cases of asthma, asthma aggravation, acute asthma attack and dyspnoea have been reported. There is limited experience from patients with asthma but latanoprost neither was found to affect pulmonary function when studied in a small number of steroid treated patients suffering from moderate asthma nor was it found to affect the pulmonary function, airway reactivity or β_2-responsiveness when studied in a small number of non-steroid treated asthma patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, no other ocular side effects of latanoprost administered at high doses are known. 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 doses of 5.5 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

In monkeys, latanoprost has been infused i.v. in doses of up to 500 μg/kg without major effects on the cardiovascular system. Intravenous administration in monkeys has been associated with transient bronchoconstriction. However, in patients with bronchial asthma, bronchoconstriction was not induced by latanoprost when administered topically to the eyes at a dose 7 times the recommended clinical dose. If overdosage with latanoprost occurs, treatment should be symptomatic.

For management of a suspected overdose, contact your local Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

The recommended dose for adults, including the elderly (over 60 years of age), is one drop in the affected eye(s) once daily. Optimal effect is obtained if LATANOPROST (latanoprost) is administered in the evening.

The dose of LATANOPROST should not exceed once daily as it has been shown that more frequent administration decreases the IOP lowering effect. Reduction of IOP in humans starts about 3 to 4 hours after treatment and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

If one dose is missed, treatment should continue with the next dose the following day.

Use in combination with other drugs

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

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Latanoprost

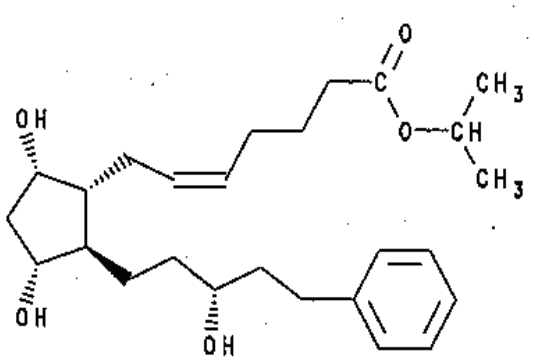
Chemical Names: 1) Isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate

2) 13, 14-dihydro-17-phenyl-18, 19, 20-trinor-$PGF_{2\alpha}$-isopropyl ester

CAS No.: 130209-82-4

Molecular Formula: $C_{26}H_{40}O_5$

Structural Formula:



Molecular Weight: 432.58 g/mol

Physical Form: Colourless to slightly yellow oil.

Solubility: Very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol, and practically insoluble in water.

Composition

Each mL of LATANOPROST sterile ophthalmic solution contains 50 µg/mL latanoprost, including the following inactive ingredients: benzalkonium chloride, dibasic sodium phosphate monohydrate, monobasic sodium phosphate monohydrate, purified water, sodium chloride. LATANOPROST is buffered to a pH of approximately 6.7 and is isotonic with lacrimal fluid.

Stability and Storage Recommendations

Store unopened bottle under refrigeration (2 to 8°C). Protect from light. Once opened, bottle may be stored at room temperature up to 25°C, for up to six weeks.

AVAILABILITY OF DOSAGE FORMS

LATANOPROST (latanoprost) is a sterile, isotonic, buffered aqueous solution of latanoprost 50 µg/mL. One drop contains approximately 1.5 µg of latanoprost. LATANOPROST is intended for topical administration on the eye. The non-medicinal ingredients are: Benzalkonium Chloride 50%*, Dibasic Anhydrous Sodium Phosphate, Monobasic Sodium Phosphate Monohydrate and Sodium Chloride.

* Benzalkonium chloride is used as 50% solution in water, containing small amounts of ethyl alcohol.

LATANOPROST is supplied in a 5 mL plastic ophthalmic dispenser bottle with a dropper tip, screw cap and tamper proof polyethylene overcap.

Each bottle contains 2.5 mL of LATANOPROST corresponding to approximately 80 drops of solution.

INFORMATION FOR THE CONSUMER

Please read this carefully before using LATANOPROST (latanoprost). It provides useful information about this medication and effects you may experience. If you have any questions or need explanations, please ask your doctor or pharmacist. Remember: This medication is prescribed for the particular condition that you have. Never give this medication to others. Do not use it for any other condition.

What kind of medication is LATANOPROST and how does it work?

LATANOPROST is a solution for use only in the eyes. The active ingredient in LATANOPROST is one of a group of medications known as prostaglandins. It helps to lower the pressure within the eye by increasing the natural outflow of fluid from inside the eye. LATANOPROST has been shown to work by itself to lower pressure in the eye.

What is LATANOPROST for?

LATANOPROST is used to treat glaucoma and ocular hypertension. Both these conditions are associated with an increase in pressure within the eye and eventually they may affect your eyesight.

What is LATANOPROST made up of?

Active Ingredients: each millilitre (mL) contains 50 micrograms of latanoprost.
Other Ingredients: benzalkonium chloride, dibasic sodium phosphate monohydrate, monobasic sodium phosphate monohydrate, purified water, sodium chloride.
Each bottle contains 2.5 mL of solution, approximately 80 drops.

Before using LATANOPROST you should tell your doctor if:

- You are allergic to any of the ingredients in LATANOPROST.
- You are using any other eye drops or taking any other medication.
- You are pregnant, think you might be pregnant or you are planning a pregnancy.
- You are breast feeding.
- You have or have had herpes simplex keratitis (inflammation of the cornea caused by the herpes simplex virus).

- Your eyes are sensitive to light.

LATANOPROST contains a preservative that may be absorbed by contact lenses and stains them a brown colour. Contact lenses can be reinserted 15 minutes after applying the eye drops.

If you are using more than one type of eye drop medication, wait at least 5 minutes between each different eye drop.

How to use LATANOPROST

One drop of LATANOPROST should be dropped into the affected eye(s) once daily. The best time to do this is in the evening.

Do not allow the dropper tip of the bottle to touch the eye or other surrounding structures, because this could contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye with subsequent loss of vision may result if you use eye drop solutions that have become contaminated. If you experience any type of eye condition or have surgery, immediately seek your doctor's advice concerning the continued use of the bottle you are using.

If you forget to use your eye drops at the usual time, wait until it is time for your next dose. If you put too many drops in your eye(s), you may feel some slight irritation.

LATANOPROST is not recommended for use in children.

Follow these steps to help you use LATANOPROST properly:

1. Wash your hands and sit or stand comfortably. If you wear contact lenses, remove them before using your eye drops.
2. Once the bottle is opened, hold it in one hand and steady your thumb against your brow or the bridge of your nose.
3. Use your index finger to gently pull down the lower eyelid of the affected eye(s) to create a pocket for the drop.

4. Gently press the side of the bottle to allow only a single drop to fall into the pocket. Do not let the tip of the bottle touch your eye.
5. Close your eye for 2 to 3 minutes.
6. If your doctor has told you to use drops in both eyes, repeat the process for the other eye. LATANOPROST should be used until your doctor tells you to stop.

Overdose

In case of drug overdose, particularly oral ingestion, contact a health care practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

What might happen while you are using LATANOPROST.

LATANOPROST may change the colour of your eye. It may make your iris (the coloured part of your eye) more brown. This happens most commonly if your iris has mixed colours, i.e., blue-brown, grey-brown, green-brown or yellow-brown. If you use LATANOPROST in one eye only, colour changes in the iris may appear only in the treated eye. These changes may be permanent.

LATANOPROST may also cause your eye lashes to darken, appear thicker and longer than they usually do and increase in number. LATANOPROST might cause eye irritation due to the growth of misdirected eyelashes; tell your doctor if this happens. A very small number of people may notice their eyelids look darker after using LATANOPROST for some time. These changes may be more noticeable if you are only treating one eye. Eyelash changes are reversible after treatment with LATANOPROST is stopped. Eyelid skin darkening may be permanent.

When using LATANOPROST, you might feel as if there is something in your eye(s). Your eye(s) might water and become red. As with other eye drops, if your vision is blurred when you first put your drops in, wait until this wears off before you drive or operate machinery. A few people using LATANOPROST have developed a skin rash.

A few people may experience changes in their vision, sometimes in combination with a red and sore/painful eye. These changes do not always occur right after administering the drops, and if they occur, you may find that reading and seeing fine details is more difficult. Although unlikely,

if you experience any of these changes, stop using LATANOPROST and contact your doctor immediately.

Be sure to tell your doctor (or pharmacist) if you notice any other unwanted side effects.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

How to store LATANOPROST.

Before LATANOPROST is first opened, keep it in a fridge (between 2°C and 8°C/36°F and 46°F), out of direct light. Once the bottle has been opened, LATANOPROST may be kept at room temperature up to 25°C. LATANOPROST must be used within 6 weeks after opening the bottle. Discard the bottle and/or unused contents after 6 weeks. LATANOPROST should not be used after the expiry date on the bottle.

Keep all medicines in a safe place, out of the reach of children.

PHARMACOLOGY

ANIMAL PHARMACODYNAMICS

Latanoprost has been shown to lower IOP in primates, with minimal acute irritation of the eye. Results from studies show large species differences in pharmacologic responses which probably depend on the variation in prostaglandin receptor distribution between species.

Reduction of IOP - Topical administration of doses of 0.3-3 µg/eye in the cat had very little IOP reducing effect. In the cynomolgus monkey, topical doses of 1-9.5µg caused dose-related reduction in IOP. The onset of effect was slow, giving a maximum reduction 4 to 6 hours after the dosing. Repeated administration of 1-3 µg latanoprost daily for 5 days, lowered IOP effectively.

Aqueous Humour dynamics: mode of action - The effect of topical treatment of latanoprost on aqueous humour dynamics was studied in cynomolgus monkeys. Latanoprost (3 µg) was applied once daily for five days, and on the fifth day of treatment the aqueous humour dynamics was determined using iodine labelled albumin as tracer. In the same experiments outflow facility was measured using a two level constant pressure infusion. Latanoprost increased the uveoscleral outflow by about 50% whereas the trabecular outflow and the outflow facility were unchanged. The total outflow tended to increase. The main mechanism for pressure reduction after treatment with latanoprost thus seems to be an increased uveoscleral outflow of aqueous humour. These results are in agreement with earlier studies with $PGF_{2\alpha}$-IE demonstrating the same main mechanism to lower IOP.

Other pharmacologic effects in the eye - In cats latanoprost had a marked pupillary constrictive effect. Topical application of 0.3-3 µg gave a dose dependent reduction of the pupillary diameter with a maximum response 2-3 hours after treatment. The miotic effect observed in cats and dogs is most probably a result of a direct effect on prostaglandin receptors in the iris sphincter muscle. In cynomolgus monkeys no miosis or a slight dilation of the pupil was seen after latanoprost treatment, and in clinical studies no change in pupil diameter has been observed during latanoprost treatment. The difference between species is probably due to different distribution of prostaglandin receptors.

Effects on airway resistance - Airway resistance was estimated from the intrathoracic inspiration/expiration pressure difference. At the two highest doses (2 µg/kg and 6 µg/kg, 50 times and 150 times the clinical dose, respectively), there was an increase in pressure difference and in respiration rate. The blood flow to the lungs also decreased after the two highest doses. This indicates most likely some degree of constriction of the bronchial tree although studies in unanesthetized animals described below showed little effect.

Cardiovascular and pulmonary effects - The effects of intravenously administered latanoprost on the cardiovascular and pulmonary system in unanesthetized cynomolgus monkeys have also been evaluated. Two male and two female cynomolgus monkeys received intravenous injections of vehicle (0.9% saline) or latanoprost at doses of 1, 10, 100 and 500 µg/kg b.w. Treatment with latanoprost was in general without consistent effects on the arterial blood pressure, but dose-related increases in heart rate were recorded in 2 out of 4 animals. Dose related increases in respiration rate were recorded in all four animals following latanoprost treatment. With the highest dose the respiration rate approximately doubled, but the animals showed no signs of dyspnea. No consistent dose related changes in ECG could be detected, but minor changes in ECG waveform were recorded in 3 of the 4 animals following doses of 100 and 500 µg/kg (2500-12,500 times the clinical dose). Minor changes in ECG were also seen after vehicle administration.

The cardiovascular effects after intravenous injection of latanoprost have been studied in cynomolgus monkeys under pentobarbital anaesthesia. Latanoprost was given in escalating doses (0.6, 2 and 6 µg/kg body weight), the lowest dose corresponding to about 15 times the clinical dose in the eye (~0.04 µg/kg b.w.). At the highest dose level (150 times the clinical dose) latanoprost induced a transient increase in blood pressure and a 30% increase in cardiac output. Regional blood flow was determined with radioactive microspheres, and in most organs only minor changes in blood flow were detected. Marked increases in blood flow were detected in the temporal, parietal and frontal lobes of the brain but only with the highest dose of latanoprost. The effect on the coronary blood flow of the heart was a dose related increase. Latanoprost had no significant effect on renal blood flow. It can be concluded that any systemic effect of latanoprost on the cardiovascular system after topical application in the eye is unlikely.

HUMAN PHARMACODYNAMICS

A double-masked study was performed which included 20 normal volunteers and 20 patients with ocular hypertension who were treated with 60 µg/mL latanoprost in one eye and placebo in the other eye twice daily for five days. Drug effects were evaluated by comparing the two eyes. Latanoprost caused no significant effect on aqueous flow. Outflow facility was determined on the fifth day of treatment and was increased, compared to the fellow eye, from 0.33 to 0.41 µL/min/mmHg in normal eyes and from 0.20 to 0.26 µL/min/mmHg in ocular hypertensive eyes. These increases were statistically significant but they are not large enough to explain the reduction of IOP. Clinical tonography can not be used to differentiate between outflow through the trabecular meshwork or the uveoscleral route, and the increase observed in outflow facility may well be explained at least partly by increased facility of the uveoscleral outflow routes.

Toris et al. (1993) have reported an attempt to determine uveoscleral flow by an indirect technique in the human eye, and they concluded that increased uveoscleral flow was the main mechanism of action also in the human eye.

The effect of latanoprost on the nocturnal IOP has been addressed in one study. Patients were hospitalized and the nocturnal IOP was constructed from several measurements at different times of different nights. Once daily administration of latanoprost 50 µg/mL in the morning reduced the nocturnal IOP to about the same extent as daytime IOP, although the IOP-reduction of 2.3 mmHg (corrected for change in fellow eye) from a baseline IOP of 23.0 mmHg in patients also treated with timolol, and of 3.5 mmHg from a baseline of 22.0 mmHg in patients with no other IOP reducing therapy, can be considered moderate.

In one study, 12 healthy volunteers and 11 asthmatic patients, 6 males and 5 females in each group, received three doses of escalating concentration 35, 115 and 350 µg/mL of latanoprost in each eye. No negative effect was observed on any of the respiratory parameters measured in either test group (one female was excluded from the study). In addition, latanoprost has not been found to affect pulmonary function when studied in a small number of steroid treated patients suffering from moderate asthma.

HUMAN PHARMACOKINETICS

The main study providing basic pharmacokinetic data included four male volunteers between 63 and 67 years of age receiving either 3 μg labelled latanoprost topically as an eye drop or 210 μg labelled latanoprost during a 15 min i.v. infusion. From this study the fate of an ocular dose can be summarized as follows: 77 to 88% is absorbed systemically, 90% is bound to plasma proteins within 3 min. A maximum plasma concentration of 64 pg/mL is reached within 40 min, and the drug and/or its metabolites is rapidly eliminated with a half-life in the β-phase of 1.84 hrs in plasma. 88% is eliminated by the kidneys, essentially all of it within 24 hrs, and 15% through faeces with a more prolonged elimination time indicating some biliary excretion of drug or metabolites (< 0.09% 144-168 hrs post-dose). Relevant corresponding figures for i.v. infusion are similar. This study is based on radio labelled latanoprost and gives no information concerning metabolism of the drug. Thus the figures should be regarded as maximal figures for active drug, before correction for protein binding. The study was performed on individuals of an age group that corresponds to glaucoma patients, but included only males.

In another study it was found that the plasma levels 5-60 min post-dose in patients treated with latanoprost for at least one year were very low. Ten patients were examined, 8 treated in both eyes, two in one eye only, all of them with a concentration of 50 μg/mL corresponding to a dose of about 1.5 μg or 3 μg latanoprost assuming total absorption of one eye drop in each eye. There were 5 males and 5 females between 64 and 81 years of age. A total of 49 blood samples were taken, five from each patient (the final 60 min sample was lacking in one patient) trough and 5, 15, 30 and 60 min values post-dose. In 30 of those 49 samples there was no measurable activity of the acid of latanoprost (< 20 pg/mL). This included all ten trough samples and the remaining four samples of three patients (two on 3 and one on 1.5 μg). In another 7 samples the detected activity was below the accepted detection limit for the technique, 30 pg/mL. The highest values observed were 5 min: 67 pg/mL, 15 min: 54 pg/mL, 30 min: 55 pg/mL, and 60 min: 42 pg/mL. Thus these data are similar to those found in the study on healthy volunteers with radio labelled latanoprost concerning maximal plasma levels.

TOXICOLOGY

Toxicological studies performed in mice, rats, rabbits, dogs and monkeys indicate that there is a high therapeutic index with latanoprost with respect to systemic side effects. The maximum clinical daily dose is expected to be 1.5 µg/eye/day.

SINGLE DOSE TOXICITY

Oral and intravenous (i.v.) single dose toxicity was studied in mice and rats. Because of low solubility in water, the maximum concentration of latanoprost in saline was 40 µg/mL and the maximum injected dose was 2 mg/kg, approximately 50,000 times the clinical dose. No mortality was observed. For oral single dose toxicity a solution of latanoprost in oil was used to achieve a higher concentration. The highest dose employed, 50 mg/kg (approx. 1 million times the clinical dose), did not induce any toxic symptoms. In an i.v. toxicity study in dogs, no mortality occured at doses of 170, 340 or 680 µg/kg. Clinical signs observed were similar to those reported after $PGF_{2\alpha}$.

REPEATED DOSE TOXICITY

Topical administration on the eye - The effect of daily administration of the latanoprost formulation topically on the eye has been investigated in a subacute study in rabbits (4 weeks) and chronic studies in rabbits and cynomolgus monkeys (12 months) and rhesus monkeys (24 months).

Studies in rabbits - In the rabbit study, eye drops containing latanoprost were administered twice daily for a total of four consecutive weeks to Fauve de Bourgogne (pigmented) rabbits, the doses being 0, 1, 5 and 25 µg per administration. The total daily dose was 0, 2, 10 and 50 µg/eye. One eye was treated and the other served as control. No local ocular irritation and no effects of treatment on the pupillary or corneal reflexes were observed. No clinical changes were observed during the ophthalmological examination and no effects of treatment of toxicological significance

were observed when clinical pathology parameters were examined. No treatment-related macroscopic or microscopic changes were observed.

In a 52-week study in Dutch belted rabbits, 4 groups of 10 rabbits of each sex received 0, 10, 30 and 100 µg/day of latanoprost by two daily ocular administrations. Latanoprost eye drops or vehicle was instilled into the conjunctival sac. Control animals received vehicle in the right eye only. Treated groups received the test formulation in the right eye and the same quantity of vehicle in the left eye. Ophthalmoscopy, tonometry and pachymetry examinations were performed on all animals pre-dose and at weeks 14, 25 and 51. No evidence of local irritancy, ocular or systemic toxicity, or change in the pigmentation of iris were observed. A mild transient erythema and equivocal variations in intraocular pressure were observed. No treatment-related macroscopic or microscopic changes were seen.

Studies in monkeys - Two 12-month topical ocular studies were completed in cynomolgus monkeys. In the first study wild caught cynomolgus monkeys were divided into 4 groups receiving 0, 20, 50 and 100 µg/day by two topical administrations. Treated animals received latanoprost solution in the right eye and the corresponding vehicle in the left eye. During the study some animals developed an increase in the iris pigmentation and an increase of the palpebral fissure and the study was therefore slightly modified. These changes started to appear in some animals after 2-3 months treatment. At the end of the treatment period, two treated males and one treated female were kept for a treatment-free period of 183 days (26 weeks); in one female the treatment was stopped on day 156 to evaluate the recovery of the ocular changes (iris pigmentation and eyelid effects) until the end of the treatment period for the other animals (week 53). No treatment-related signs of toxicity were seen at any dose level. The only treatment-related findings were reversible changes in the aspect of the palpebral fissure and a non-reversible increase in the iris pigmentation. These changes were attributed to the pharmacological action of latanoprost and were without a clear dose-relationship in frequency or intensity. No pathological changes were observed in any of the intra- or extraocular tissues at microscopic examination. The iridial stroma exhibited a more intense pigmentation of the melanocytes but remained morphologically normal. These findings were further confirmed in extended morphological studies of the treated and control cynomolgus monkey eyes.

In a 52-week study in domestic bred cynomolgus monkeys, lower doses compared with the above mentioned study were used since clinical studies had indicated that the maximum human dose would be 1-2 µg/eye/day. The same experimental procedure as in the above mentioned study was employed. Two groups of five animals of each sex were treated with 2 and 6 µg/day by twice daily applications. Six monkeys served as control and received the vehicle only. Also in this study no treatment-related signs of toxicity were observed at any dose level. The only treatment-related findings were the same local ophthalmological changes in the treated eye as described above. These consisted of a change in the aspect of the palpebral fissure (one male at 6 µg/eye/day) and a slight increase in the iris pigmentation in the majority of animals. With the lower doses the changes appeared later, usually between 6-12 months of treatment.

Another chronic study was conducted in domestic bred rhesus monkeys to investigate the toxicity of latanoprost following two daily ocular administrations for 104 consecutive weeks with an intermediate sacrifice after 52 weeks of treatment. To evaluate the regression of any toxic signs, some animals treated for 52 weeks were left for a two-year treatment-free period. The monkeys were divided into 4 groups receiving 0, 1, 3 or 10 µg, by twice daily applications (i.e., 0, 2, 6 or 20 µg/day). No treatment related signs of toxicity were observed at any dose level. The only treatment related findings were local ophthalmologic changes in the treated eye confirming observations made in the cynomologus monkey: a dose-dependent reversible slight increase of the palpebral fissure (6 and 20 µg/day), and a slight increase in iris pigmentation in some animals from all dose groups without a dose-relationship in frequency and intensity, but with a trend regarding time of appearance. During the second year of treatment, new cases of pigmentation were observed only in the high dose group. Microscopic examination revealed a slight increase in frequency and intensity in animals receiving 6 and 20 µg/day. The iridial stroma exhibited a more intense pigmentation of the pigmented cells but remained morphologically normal. There were no signs of increased number of pigmented cells of the iris stroma. These changes were attributed to the pharmacological action of latanoprost, as no pathological changes were observed in any of the intra- or extraocular tissues.

Iris pigmentation - A number of studies have been performed to investigate the mechanism of latanoprost induced iris pigmentation. It is of particular interest that naturally occurring

prostaglandins such as $PGF_{2\alpha}$ and PGE_2 also cause increased pigmentation of the iris. The effect is a class effect of prostaglandins. It has been shown that the human iridial melanocytes express FP receptors in their cell membrane, and since latanoprost is a very selective FP receptor agonist, it implies that the effect is mediated by FP receptors in the melanocytes. Latanoprost binds only to a very small extent to melanin.

Morphometrical analysis of irides from monkeys in the chronic toxicity studies has demonstrated that there was no increase in the number of iridial melanocytes in the treated eyes compared to controls nor was latanoprost-induced increased iris pigmentation in sympathectomized rabbits associated with any increase in the number of stromal melanocytes or other cells in the iris. No proliferative effect of latanoprost acid has been demonstrated in *in vitro* studies on cultured human melanocytes and epidermal melanocytes and there was no uptake of 5-bromodeoxyuridine (5-BrU) or tritiated thymidine into melanocytes incubated with latanoprost acid, which strongly indicate that DNA synthesis has was not initiated during exposure to latanoprost. Additionally, latanoprost had no proliferative effect on human cultured uveal and cutaneous melanoma cell lines, implying that latanoprost does not enhance proliferation of malignant melanoma cells. The results of these *in vivo* and *in vitro* studies on monkey and human melanocytes clearly show that latanoprost has no proliferative effect on ocular melanocytes.

The melanogenic effect of latanoprost has been investigated in several studies. It has been shown that the eumelanin (physiological brown melanin) content of the iris stroma increased significantly during latanoprost treatment in cynomolgus monkeys, whereas the normally predominant pheomelanin (cystein-containing yellowish melanin) was unaffected by treatment. Since pheomelanin cannot be converted to eumelanin, the only possibility is the new syntheses of eumelanin.

A morphometrical analysis of iridial melanocytes from rhesus monkeys treated for two years with latanoprost demonstrated that there was an increase in the number of melanosomes and the area covered by melanosomes of the cytoplasm in the treated eye compared to the contralateral control eye.

Latanoprost has been shown to increase the transcription of tyrosinase, the rate-limiting enzyme in the biosynthesis of melanin, in iridial melanocytes *in vivo* in monkeys and also in cultured human melanocytes from mixed colour (hazel) and brown irides. These results also suggest that the basal transcription of tyrosinase may be of importance whether latanoprost treatment leads to an increase in tyrosinase expression and that latanoprost probably contributes to the variability of the latanoprost-induced iris pigmentation change. This may explain why increased pigmentation in blue eyed persons during latanoprost treatment only rarely is seen or is very slow.

Latanoprost has no melanogenic effect on melanocytes in the iridial and retinal pigment epithelium of the monkey eye.

The available data demonstrate that latanoprost induces melanogenesis thereby increasing the melanin content of the iridial melanocytes and exclude that proliferative changes occur during pigmentation. Decreased catabolism of melanin in the iridial melanocytes is considered an unlikely mechanism behind the latanoprost-induced increased iridial pigmentation, since there seems to be no or minimal catabolism of melanin in iridial melanocytes.

Light microscopical and ultrastructural examinations of human iridectomy and trabeculectomy specimens have demonstrated that the latanoprost-induced pigmentation change is not associated with any proliferative, inflammatory or degenerative changes in latanoprost-treated irides or hyperpigmentation in the trabecular meshwork.

Oral repeated dose administration - Subchronic oral administration of latanoprost was performed in mice and rats with latanoprost dissolved in saline and oil (neutral oil TG/10). Due to low solubility the maximum dose of latanoprost in saline was 200 µg/kg/day, approximately 5000 times the clinical dose, and the maximum dose in oil solutions was 10 mg/kg/day, approx. 250,000 times the clinical dose. The studies in mice and rats were 28 days and 13 weeks, respectively. No toxic effects were seen.

Intravenous repeated dose administration - The studies were performed in rats and dogs, the duration of treatment being 4 and 13 weeks in each species. Latanoprost was dissolved in saline and in the 4 week study in rats injected in doses of 1, 10, 100 and 340 µg/kg/day. In the 13 week

study in rats the doses were 5, 35 and 250 µg/kg/day. In the intravenous studies some mortalities occurred in rats given 250 µg/kg/day (> 5000 times the clinical dose per body weight). The mortalities were most likely due to acute cardiovascular effects.

In the 4 week dose-finding study in the dog in which doses of 1, 10, 100 and 340 µg/kg/day were tested, doses of 100 and 340 µg/kg caused vomiting, hypersalivation and miosis. The doses selected for the 13 week study were 1, 10 and 100 µg/kg/day. Hypersalivation and miosis were seen at the dose of 10 and 100 µg/kg/day, and vomiting at the dose of 100 µg/kg. No pathological changes were observed. It is evident that a doses of 250 µg/kg/day causes some deaths due to cardiovascular effects in rats. The high doses employed are considerably higher (5000 - 10,000 times) than the clinical dose.

REPRODUCTION AND TERATOLOGY

In order to reveal potential adverse effects on reproduction, latanoprost has been administered i.v. to male and female rats before and during pregnancy to study its effect on fertility, teratology and peri- and postnatal development. All studies were performed with intravenous injection of latanoprost since this route of administration was considered to give the highest systemic exposure. The duration of administration of latanoprost was selected to cover the periods where reproductive performance/fertility, embryogenesis and peri/postnatal development are known to be sensitive to drug effects in the respective species. The doses were selected based on dose-range finding studies in rats and rabbits and on the results from preliminary systemic toxicity studies in rats.

The fertility and the general reproductive performance were not affected in female or male rats. In the dose range study for peri- and postnatal toxicity, pup mortality was increased in the groups given 10 µg/kg or more and this effect was particularly marked in the 100 µg/kg/day group. The high dose selected was 10 µg/kg in the main peri- and postnatal study in the rat. This study showed no treatment-related effects on peri- and postnatal development at the selected dose levels (1-10 µg/kg/day) of latanoprost.

In the embryotoxicity study in rats, no embryotoxicity was observed at the doses (5, 50 and 250 µg/kg/day) of latanoprost used. However, latanoprost induced embryolethal effects in rabbits in doses above 5 µg/kg/day. The dose level of 5 µg/kg/day caused a slight increase in foetal resorption and was selected as the high dose in the main study. This dose caused significant embryo-foetal toxicity characterized by increased incidence of late resorption and abortion and by reduced foetal weight. No consistent indications of embryo fetal toxicity were observed with the low and intermediate doses of 0.2 and 1 µg/kg/day. The effects on the foetal development are probably due to a pronounced luteolytic effect in the rabbit which has been described as a pharmacologic property of prostaglandin F2α and its analogues and has been reported in several research and review papers.

The feto-placental transfer and lacteal secretion of latanoprost was investigated in rats. The concentrations of radioactivity of latanoprost and PhXA85 (acid of latanoprost) were measured in plasma and milk. The concentration of radioactivity was analysed in tissues after single intravenous administration of tritium labelled latanoprost at a dose of 200 µg/kg to pregnant or

lactating rats. On the 12th-gestation day, the concentration of radioactive latanoprost in the fetus was 0.00006% of the dose at 1 hour. The value of radioactivity in the fetus at 24 hours was below the limit of detection. On the 18th gestation day, the concentration of radioactive latanoprost in the fetus was 0.018% (at 1 hour) and 0.005% (at 4 hour). Again, at 24 hours there was no radioactivity measured. In the milk the concentration of radioactive latanoprost was shown to be eliminated more slowly than for plasma. Of the low levels remaining in milk at 2 hours and 8 hours, only 5.5% and 15% respectively was the acid of latanoprost. The more polar metabolites formed the rest of the radioactivity in the milk.

MUTAGENICITY

Studies on the mutagenic potential of latanoprost have been performed by using *in vitro an*d *in vivo* methods.

The *in vitro* mutagenic potential was tested in bacteria (Salmonella typhimurium and Eschericia coli) and in the mouse lymphoma cells. No mutagenic effect was observed in these systems. *In*

vitro chromosome aberration studies in human lymphocytes showed an increase in numbers of aberrant cells at concentrations of 130 and 160 µg/mL in the absence of S9. Treatment of cultures with latanoprost in the presence of S9 were negative. Normal frequencies of cells with aberrations were seen at a concentration of 100 µg/mL. The cytotoxic effects of latanoprost were clearly reflected by the poor yield of cells from cultures receiving 160 µg/mL in the absence of S9.

The *in vivo* micronucleus test in mice showed no signs of chromosome aberrations. As the aberrations in the mouse lymphoma occur predominantly in the absence of S9, the performed micronucleus test constitutes an appropriate *in vivo* assessment.

In order to further elucidate a potential genotoxic effect, an *in vitro/in vivo* unscheduled DNA test (UDS) was performed. This study did not indicate any mutagenic potential of latanoprost and as the test is a validated method it can be concluded that latanoprost has no mutagenic potential.

CARCINOGENICITY

For the evaluation of the carcinogenic potential, latanoprost dissolved in physiological saline was administered by gavage route to mice and rats. The duration of the study in mice was intended to be 80 weeks. However, owing to the good survival rate of the animals, the duration of the study was extended until survival had reached approximately 50% for each sex. The males were necropsied week 88, and the females week 92. The dose levels (2, 20 and 200 µg/kg/day) were chosen based on the human therapeutic dose level and previous toxicity and pharmacokinetic studies. The highest dose is approx. 5000 times the human therapeutic dose when normalized for body weight and approaches the limit of solubility of latanoprost in water. In a toxicokinetic study in the same strain of mouse, latanoprost administered at 200 µg/kg/day once daily by oral gavage resulted in a mean maximal plasma concentration of the acid of latanoprost 5 min after the last dose about 50 times higher than the maximal human plasma concentration after a clinical dose in both eyes.

There were no clinical signs attributable to treatment and no evidence to suggest that treatment had any effect on the incidence of palpable masses. Survival was not affected by treatment with

the test article. The incidence and causes of morbidity and mortality in all groups were consistent with the expected profile in this strain of mouse. Body weight for high dose females tended to be slightly lower than for those of the control throughout the study. There was no indication that red or white blood cell counts were affected by treatment. The spectrum of necropsy findings in treated animals was generally similar to that in controls. There were no non-neoplastic findings of unusual nature or incidence attributable to the test article. There were no unusual tumour types or increased incidence of tumours attributable to the test article. It is therefore evident that the latanoprost has no carcinogenic potential in the mouse.

The design of the carcinogenicity study in rats was the same as in mice but with longer duration of the study. The dose levels were based on the human therapeutic dose level and previous toxicity and pharmacokinetic studies. The high dose, 200 µg/kg/day, was approximately 5000 times the human therapeutic dose and approaches the limit of latanoprost solubility in water. In a toxicokinetic study in the same strain of rats, latanoprost was administered at 200 µg/kg/ day once daily by oral gavage route, the maximal plasma concentration of the acid of latanoprost was about 13-17 times higher than the maximal human plasma concentration after a clinical dose on both eyes. Therefore in the rat a sufficient dose level was used.

There were no clinical signs attributable to treatment and no evidence to suggest that treatment had any effect on the incidence of palpable masses. There was no indication that survival had been adversely affected by treatment. The incidence and causes of morbidity and mortality in all groups were consistent with the expected profile in this strain of rat. Body weight and food consumption were not affected by treatment. There was no indication that red or white blood cell counts were affected by treatment. The spectrum of necropsy findings in treated animals was generally similar to that in controls. There were no unusual non-neoplastic findings or increased incidence of tumours attributable to the test article. It can therefore be concluded that the oral administration of latanoprost to the rat, for the major part of its life span, at dose levels up to 200 µg/kg/day was well tolerated and produced no evidence of toxicity. There were no unusual tumour types attributable to the test article. Therefore in the rat no carcinogenic potential was observed.

SPECIAL TOXICITY

An eye irritation test was conducted in rabbits in order to study whether changes in the formulation of the eye drops resulted in any local irritating effect. The two formulations tested were non-irritant. It can be stated that the formulations have been well tolerated in all the topical eye studies.

The anaphylactic and sensitization studies in the guinea pig demonstrated that latanoprost did not have any sensitization properties.

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