

PRODUCT MONOGRAPH
INCLUDING CONSUMER INFORMATION

Pr**MONOPROST**[®]

Latanoprost Ophthalmic Solution

50 µg/mL
(Sterile, preservative-free, single-dose container)

Prostaglandin F_{2α} analogue

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Pr**MONOPROST**[®]

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50 µg/mL
(Sterile, preservative-free, single-dose container)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution / 50 µg/mL latanoprost	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

MONOPROST[®] (latanoprost ophthalmic solution), 50 µg/mL [preservative-free] is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Geriatrics (> 65 years of age):

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Pediatrics (<18 years of age):

MONOPROST[®] is not recommended for use in children or adolescents as the safety and efficacy of MONOPROST[®] has not been established in this population.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Latanoprost has not been studied in patients with hepatic impairment. Caution is advised if using MONOPROST® in patients with hepatic impairment.

Ophthalmologic

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. Caution is advised if using MONOPROST® in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

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). This change may not be noticeable for several months to years.

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.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes can include increased length, thickness, pigmentation, and number of lashes or hairs, as well as misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

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 and/or pigmentary glaucoma patients.

Latanoprost is not recommended in patients with active intraocular inflammation (i.e., iritis/uveitis). Caution is advised if using MONOPROST® in patients with a history of intraocular inflammation. Latanoprost is not recommended in patients with active herpes simplex keratitis or a history or recurrent herpetic keratitis specifically associated with prostaglandin analogues. Caution is advised if using MONOPROST® in patients with a history of herpetic keratitis.

Contact lenses should be removed prior to the administration of latanoprost, and may be reinserted 15 minutes after administration.

Renal

Latanoprost has not been studied in patients with renal impairment. Caution is advised if using MONOPROST® in patients with renal impairment.

Respiratory

There is limited experience with latanoprost in patients with asthma or chronic obstructive pulmonary disease; however, rare cases of exacerbation of asthma and/or dyspnoea were reported from post

marketing experience. Caution is advised if using MONOPROST® in patients with asthma or chronic obstructive pulmonary disease. (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Special Populations

Pregnant Women: 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 (see TOXICOLOGY). Caution is advised if using MONOPROST® in pregnant women.

Nursing Women:

Latanoprost and its metabolites may pass into breast milk. Caution is advised if using MONOPROST® in nursing women.

Pediatrics (<18 years of age):

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Ocular adverse events in either MONOPROST® or XALATAN™ groups were primarily considered by the investigators to be of mild intensity and did not require treatment intervention. One adverse event of ocular discomfort was classified as severe in a patient treatment with MONOPROST®. No ocular adverse event was considered serious. Ocular adverse events infrequently caused drug withdrawal, regardless of treatment group. The most common adverse events in the MONOPROST® group from clinical trials were blepharitis, conjunctival hyperemia, instillation site pain and instillation site pruritus.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of MONOPROST® (latanoprost ophthalmic solution) 50 µg/mL w/v [preservative-free] was assessed in a pivotal phase III, randomized, investigator-masked, positive-controlled clinical study [LT2345-PIII-12_08] containing 402 patients (mean age ± SD of 64.7 ± 11.5 years) with a history of elevated intraocular pressure. MONOPROST®, in contrast to the positive control XALATAN™ (latanoprost ophthalmic solution) 50 µg/mL, does not contain the preservative benzalkonium chloride (BAK). MONOPROST® was administered to 213 patients at a dose of one drop daily in the evening for up to 3 months. The most frequent adverse events observed in the clinical trial are provided in Table 1.

Table 1: Adverse events (related and unrelated) reported in $\geq 1\%$ of subjects treated with either MONOPROST® or XALATAN™ in the pivotal phase III clinical study [LT2345-PIII-12_08]

System Organ Class† Preferred Term	MONOPROST® (N=213) n (%) of subjects	XALATAN™ (N=189) n (%) of subjects
Any AE	12 (5.6)	28 (14.8)
Eye disorders	8 (3.8)	14 (8.3)
Conjunctival hyperaemia	1 (0.5)	3 (1.6)
Conjunctivitis allergic	1 (0.5)	3 (1.6)
Vision blurred	1 (0.5)	3 (1.6)
Corneal staining	1 (0.5)	2 (1.1)
Dry eye	1 (0.5)	2 (1.1)
Eye pain	0 (0.0)	2 (1.1)
Foreign body sensation	1 (0.5)	2 (1.1)
Photophobia	1 (0.5)	2 (1.1)
Punctate keratitis	1 (0.5)	2 (1.1)
General disorders and administration site conditions	1 (0.5)	4 (2.1)
Drug intolerance‡	1 (0.5)	4 (2.1)
Infections and infestations	1 (0.5)	8 (4.2)
Bronchitis	0 (0.0)	3 (1.6)
Urinary tract infection	0 (0.0)	3 (1.6)
Tooth infection	1 (0.5)	2 (1.1)
Nervous system disorders	2 (0.9)	6 (3.2)
Headache	2 (0.9)	4 (2.1)
Dizziness	0 (0.0)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (1.1)
Oropharyngeal pain	0 (0.0)	2 (1.1)
Vascular disorders	0 (0.0)	2 (1.1)
Hypertension	0 (0.0)	2 (1.1)

† MedDRA version 12.0

‡ 8 AEs of drug intolerance reported by 4 subjects treated with XALATAN™.

An additional supportive phase III, randomized, investigator-masked, positive-controlled clinical study [T-2345-001 [US]] was performed in 335 patients treated with MONOPROST® or XALATAN™. MONOPROST® was administered to 166 patients at a dose of one drop daily in the evening for up to 3 months. The most frequent adverse events observed in the clinical trial are provided in Table 2.

Table 2: Adverse events (related and unrelated) reported in $\geq 1\%$ of subjects treated with either MONOPROST® or XALATAN™ in the additional phase III clinical study [T-2345-001[US]]

System Organ Class† Preferred Term	MONOPROST® (N=166) n (%) of subjects	XALATAN™ (N=169) n (%) of subjects
Any AE	19 (11.4)	35 (20.7)
Eye disorder	7 (4.2)	19 (11.2)
Conjunctival hyperemia	3 (1.8)	4 (2.4)
Blepharitis	2 (1.2)	5 (3.0)
Punctate keratitis	1 (0.6)	5 (3.0)
Vitreous detachment	1 (0.6)	2 (1.2)
Conjunctival cyst	0 (0.0)	2 (1.2)
Conjunctival hemorrhage	0 (0.0)	2 (1.2)
Conjunctivitis allergic	0 (0.0)	2 (1.2)
General disorders and administration site conditions	4 (2.4)	10 (5.9)
Instillation site pain	3 (1.8)	8 (4.7)
Instillation site pruritus	2 (1.2)	1 (0.6)
Instillation site abnormal sensation	1 (0.6)	2 (1.2)
Instillation site complication	0 (0.0)	2 (1.2)
Infections and infestations	7 (4.2)	6 (3.6)
Urinary tract infection	3 (1.8)	0 (0)
Sinusitis	2 (1.2)	0 (0)
Bronchitis	1 (0.6)	2 (1.2)
Nasopharyngitis	1 (0.6)	2 (1.2)
Herpes Zoster	0 (0.0)	2 (1.2)
Musculoskeletal and connective tissue disorders	3 (1.8)	5 (3.0)
Back pain	2 (1.2)	1 (0.6)
Sciatica	1 (0.6)	2 (1.2)
Muscle spasms	0 (0.0)	2 (1.2)

† MedDRA version 15.0

Additional adverse events ($\geq 1\%$) reported in subjects treated with XALATAN™ that may occur with MONOPROST® from clinical studies:

Eye disorders: eyelid edema, eyelid pain;

Skin and subcutaneous tissue disorders: dermatitis allergic, rash.

Ocular symptomology and signs

MONOPROST® was associated with fewer subjective symptoms of burning/stinging upon instillation and irritation/burning/stinging not upon instillation compared to XALATAN™. MONOPROST® was also inconsistently associated with fewer subjective symptoms of pruritus compared to XALATAN™. The relatively small frequency of symptoms and predominance of those reported as “present but not disturbing” suggests these symptoms have limited clinical meaningfulness.

No clinically meaningful differences in frequency of palpebral abnormality, folliculo-papillary conjunctivitis, anterior chamber flare, corneal staining punctuations, iris pigmentation modification, abnormal eyelash aspect/hypertrichosis, or abnormal palpebral skin colouration was observed in patients treated with MONOPROST® compared to XALATAN™. There was no clinically meaningful difference between treatment groups in mean cup-to-disk ratio or best far corrected visual acuity.

Less Common Clinical Study Ocular Adverse Events (Related and Unrelated) (<1%)

Eye disorders: arthropod bite, blepharoplasty, chalazion, conjunctival deposit, conjunctival disorder, conjunctival edema, conjunctival follicles, conjunctivitis, corneal disorder, diplopia*, discharge from the eye*, distichiasis, ectropion, erythema of eyelid, eye allergy, eye color change, eye irritation, eye pruritus, eyelid margin crusting, eyelids pruritus, eyelid sensory disorders, glaucoma, hordeolum, keratitis, lacrimation increased, lenticular opacities, meibomianitis, ocular discomfort, ocular hyperemia, optic disc hemorrhage, pseudoexfoliation syndrome, retinal degeneration, trichiasis, visual impairment;

Extremely rare reports of the following: retinal artery embolus*, retinal detachment*, and vitreous hemorrhage from diabetic retinopathy*.

* Additional AE from XALATAN™ product monograph¹

Less Common Clinical Study Non-Ocular Adverse Events (Related and Unrelated) (<1%)

Cardiac disorders: palpitations, tachycardia;

Ear and labyrinth disorders: tinnitus, vertigo;

Endocrine disorders: hypothyroidism;

Gastrointestinal disorders: abdominal pain, constipation, dental caries, diverticulum, gastritis, gastroesophageal reflux disease, intestinal polyp, loose tooth, nausea, pancreatitis, toothache, vomiting;

General disorders and administration site conditions: asthenia, chest pain, influenza like illness, instillation site dryness, instillation site erythema, instillation site foreign body sensation, instillation site lacrimation, pain;

Hepatobiliary disorders: cholecystitis acute, cholelithiasis;

Infections and infestations: acute sinusitis, cystitis, ear infection, gastroenteritis, infection, influenza, laryngitis, paronychia, pneumonia, sepsis, tonsillitis, tooth abscess, upper respiratory tract infection;

Injury, poisoning and procedural complications: corneal abrasion, excoriation, fibula fracture, head injury, joint sprain, laceration, post-traumatic neck syndrome, thoracic vertebral fracture, tibia fracture, traumatic arthropathy, wound dehiscence;

Investigations: visual field tests abnormal, vital dye staining cornea present

Metabolism and nutrition disorders: gout, hypoglycemia, hypokalemia, hypercholesterolemia, type 2 diabetes mellitus;

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, compression fracture, costochondritis, haemarthrosis, intervertebral disc protrusion, muscle contracture; muscular weakness, musculoskeletal pain, spinal compression fracture, spinal osteoarthritis, temporomandibular joint syndrome, torticollis;

Neoplasms benign, malignant and unspecified (incl cysts and polyps): metastatic malignant melanoma, papilloma conjunctival;

Nervous system disorders: migraine, neuropathy peripheral, syncope;

Psychiatric disorders: insomnia, major depression;

Renal and urinary disorders: hypertonic bladder, renal colic;

Reproductive system and breast disorders: ovarian cyst, pelvic mass;

Respiratory, thoracic and mediastinal disorders: chronic obstructive pulmonary disease; cough, rhinitis allergic, rhinitis seasonal, sinus congestion;

Skin and subcutaneous tissue disorders: dermatitis bullous, eczema, hair growth abnormal, ingrowing nail, pruritus, skin nodule, swelling face;

Surgical and medical Procedures: sinus operation;

Vascular disorders: basal ganglia stroke.

Post-Market Adverse Drug Reactions

In addition to the Clinical Study Adverse Events that are already listed under Table 1, 2 or list of Less Common Adverse Events above, the following adverse reactions have been identified during post-marketing use of MONOPROST® in clinical practice:

Eye disorders: Corneal edema; growth of eyelashes; keratitis, macular edema; periorbital edema;

Infections and infestations: Ophthalmic herpes simplex;

Respiratory, thoracic and mediastinal disorders: Asthma; dyspnoea;

Skin and subcutaneous tissue disorders: Skin discolouration.

Additional adverse events that have been identified during post-marketing use of BAK-preserved latanoprost in clinical practice that may occur with MONOPROST®:

Eye disorders: Eyelash thickening; eyelash hyperpigmentation; iris cyst; iritis; lid sulcus deepened; trichiasis; uveitis;

Skin and subcutaneous tissue disorders: Hypertrichosis; skin reaction; toxic epidermal necrolysis.

As these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be accurately made.

DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost. If such drugs are used concomitantly with MONOPROST®, treatments should be administered with an interval of at least 5 minutes between applications.

There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogs. The use of two or more prostaglandins, prostaglandin analogs, or prostaglandin derivatives is not recommended.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Optimal effect is obtained when MONOPROST® is administered in the evening.

Recommended Dose and Dosage Adjustment

Recommended dosage for adults – including the elderly (>65 years of age) – is one drop in the affected eye(s) once daily. The dose of MONOPROST® 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.

Missed Dose

If one dose is missed, treatment should continue with the next dose as scheduled.

Administration

MONOPROST® is for ocular use only.

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This step should be performed immediately following the instillation of MONOPROST®.

Contact lenses should be removed before instillation of MONOPROST®. Contact lenses may be reinserted 15 minutes after instillation.

For single use only. The single-dose container provides enough solution to treat both eyes once. Use one drop to treat one eye. Use one drop in each eye if treating both eyes. Discard unused portion even if treating one eye.

Patients should be instructed to:

- avoid contact between the dropper tip and the eye or eyelids;
- use the eye drops solution immediately after first opening the single-dose container; and
- discard the single-dose container after use.

Use in combination with other drugs

MONOPROST® 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.

OVERDOSAGE

For management of a suspected drug overdose, particularly accidental oral ingestion, contact your regional Poison Control Centre.

Apart from ocular irritation and conjunctival or episcleral hyperemia, no other ocular adverse event of latanoprost administered at high doses in humans are known. Intravenous infusion of up to 3 µg/kg latanoprost in healthy volunteers – mean plasma concentrations 200 times higher than that observed during clinical treatment – did not result in observed adverse events. Intravenous doses of 5.5 to 10 µg/kg resulted in observed adverse events of abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

In monkeys, latanoprost has been infused intravenously in doses of up to 500 µg/kg without major adverse effects on the cardiovascular system. Intravenous administration in monkeys has been associated with transient bronchoconstriction. 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 MONOPROST® occurs, treatment should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MONOPROST®, a prostaglandin F_{2α} (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester) analogue, is a selective prostanoid FP receptor agonist that reduces intraocular pressure by increasing the outflow of aqueous humour. Studies in animals and humans indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (i.e., decrease in outflow resistance) has also been reported in humans.

Pharmacodynamics

Reduction of intraocular pressure following a single dose in humans starts approximately 3 to 4 hours following topical administration, with maximum effect reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

Pharmacokinetics

The pharmacokinetics of latanoprost from MONOPROST® and XALATAN™ were assessed in a phase II controlled clinical study conducted in 30 patients newly diagnosed with open-angle glaucoma or ocular hypertension¹. At each assessed time point (0, 5, 10, 15, and 30 min after instillation), the number of patients with values below the limit of quantitation (LOQ: 40.0 pg/mL) was similar between groups; except at 5 min after instillation. C_{max} was marginally lower and t_{max} marginally higher after MONOPROST® suggesting MONOPROST® absorption is marginally slower than XALATAN™; however, this difference is not considered to be clinically relevant.

Table 3: Latanoprost plasma pharmacokinetic parameters following administration of MONOPROST® and XALATAN™ ophthalmic solution, 50 µg/mL in patients following 6 weeks of treatment

Treatment	C _{max} (pg/mL)	T _{max} (min)	AUC _{0-30min} (pg•min/mL)	t _{1/2} (min)
Latanoprost (MONOPROST®)	46 (20, 140)	11 (5, 15)	992 (600, 2874)	NA
Latanoprost (XALATAN™)	62 (20, 198)	7 (5, 10)	1203 (600, 3341)	NA

Limit of Quantification (LOQ) was 40 pg/mL;

Samples below LOQ were assigned a value of 20 pg/ml – trend consistent at assigned values of 0, 20, and 39 pg/mL;

Pharmacokinetic parameters are presented as geometric means;

Values in parentheses are (minimum, maximum) values for respective parameter.

t_{1/2} was not calculated as too many values were missing (values below the LOQ).

Absorption: Latanoprost is an isopropyl ester prodrug that 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 2 hours after topical administration. Systemic absorption of latanoprost is very low; 30 minutes after instillation, plasma concentrations were below the level of quantification (i.e., 40 pg/mL).

Distribution: Following topical administration in monkeys, latanoprost is primarily distributed in the anterior segment of the eye, including the conjunctiva and eyelids, while minute quantities are detected in the posterior segment.

Metabolism: There is practically no metabolism of latanoprost acid in the eye. Plasma clearance is rapid and metabolism 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 weak or no biologic activity.

Excretion:

The metabolites 1,2-dinor and 1,2,3,4-tetranor were excreted primarily in urine.

STORAGE AND STABILITY

Store MONOPROST® unopened between 15 and 25°C. After opening of the sachet, use the single-dose containers within 7 days. After opening of the single-dose container, use immediately and discard the single-dose container after use. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MONOPROST[®] (latanoprost ophthalmic solution), 50 µg/mL [preservative-free] is supplied in LDPE single-dose containers. Each single-dose container holds 0.2 ml of preservative-free latanoprost solution to deliver one drop per eye. Five single-dose containers are packaged in individual paper-aluminium sachets. Sachets are packaged in groups of 6 or 18 (i.e., 30 or 90 single-dose containers) per box.

Non-medicinal ingredients include: carbomer 974 P, disodium edetate, macrogol 4000, macrogolglycerol hydroxystearate 40, sodium hydroxide (to adjust pH), sorbitol, and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

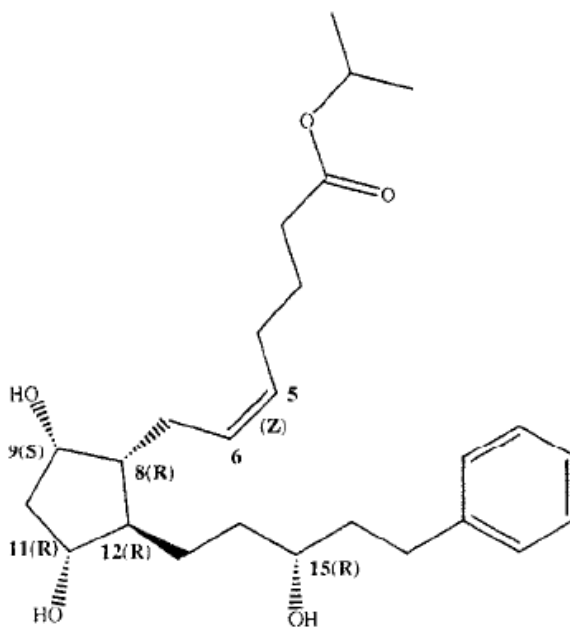
Proper name: Latanoprost

- Chemical names:
- 1) Isopropyl (Z)-7-[(1R, 2R, 3R, 5S)-3, 5-Dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate
 - 2) [1R-[1 α (Z), 2 β , 3 α , 5 α]]-7-[3,5-Dihydroxy-2-(3-(R)-hydroxy-5-phenylpentyl)-cyclopentyl]-5-heptenoic acid 1-methylethyl ester
 - 3) 13, 14-Dihydro-17-phenyl-18, 19, 20-trinor-PGF₂ α isopropyl ester

Molecular formula: C₂₆H₄₀O₅

Molecular mass: 432.6 g/mol

Structural formula:



Physical Form: Clear colourless to slightly yellow oil

Solubility: Latanoprost is freely soluble in acetonitrile, dimethyl formamide, tert-butylmethyl ether, ethyl acetate, isopropanol, methanol and methylene chloride and is practically insoluble in water and heptane.

Optical rotation: The optical rotation is determined as $+34.5^{\circ} \pm 2.5^{\circ}$.

CLINICAL TRIALS

The efficacy and safety of MONOPROST® (latanoprost ophthalmic solution) 50 µg/mL [preservative-free] was primarily evaluated in two controlled clinical studies assessing the non-inferiority of MONOPROST® compared to XALATAN™ (Table 4). A supplementary controlled clinical study performed separately provided complementary evidence of the diurnal IOP reduction due to MONOPROST®.

Study demographics and trial design

Table 4. Summary of patient demographics for clinical trials in patients with open-angle glaucoma or ocular hypertension

Study	Trial design	Dosage, route of administration, and duration	Study subjects† (n=number)	Mean age† (Range)	Baseline IOP (mmHg)‡
LT2345-PII-10/07	Multicentre, randomized, investigator-masked, crossover, active control	MONOPROST®: 1 drop QID XALATAN™: 1 drop QID 6 weeks / 6 weeks	30 21 Male 9 Female	50.7 (31-81)	22.7 ± 3.0
LT2345-PIII-12/08	Multicentre, randomized, investigator-masked, parallel, active control	MONOPROST®: 1 drop QID XALATAN™: 1 drop QID 3 months	402 202 Male 200 Female	64.7 (24-93)	24.1 ± 1.8
LT-2345-001 [US]	Multicentre, randomized, observer-masked, parallel, active control	MONOPROST®: 1 drop QID XALATAN™: 1 drop QID 3 months	335 130 Male 205 Female	66.6 (30-95)	MONOPROST®: 19.0 ± 3.2 XALATAN™: 19.5 ± 3.0

† Based on safety population.

‡ Based on per protocol population.

In the combined safety population (N=767), age ranged from 24 to 95 years, with an overall mean of approximately 65 years. Slightly more of the patients in the three studies were female than male (54.0% versus 46.0%, respectively).

In the phase II study, the inclusion criteria consisted of adults with a diagnosis of primary open angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension, with an IOP value between 22 to 30 mmHg in at least one eye. The inclusion criteria in both phase III studies consisted of adults with a diagnosis of primary open angle glaucoma or ocular hypertension with IOP treated and adequately

controlled (IOP \leq 18 mm Hg) with latanoprost 50 μ g/mL ophthalmic solution monotherapy. In these studies, following a run-in period (including a few days not on therapy just before baseline), patients enrolled were required to have at baseline an IOP $<$ 34 mmHg in both eyes and IOP \geq 22 mmHg in the eligible eye(s) for LT2345-PIII-12/08, and mean IOP \leq 28 mm Hg for LT-2345-001 [US].

The main efficacy endpoint for LT2345-PII-10/07 was an assessment of mean diurnal IOP change from baseline at 6 weeks. For the phase III studies, the main efficacy criteria were the change from baseline in IOP (measured at 9 am in LT2345-PIII-12/08 and at 8 am, 10 am, and 4 pm in LT-2345-001 [US]) after 2 weeks, 6 weeks and 3 months of treatment.

Study Results

Phase II - LT2345-PII-10/07

Intraocular pressure (IOP) was measured in the worst eye at 8 am, 12 pm, 4 pm, and 8 pm, after 6 weeks of treatment. Both treatments significantly lowered IOP at all time points compared to baseline with mean diurnal reductions of 27%, respectively. No between-treatment, period, or sequence effects were detected. The upper limit of the 95% confidence interval for the estimated mean difference between MONOPROST® and XALATAN™ was lower than the non-inferiority margin of 1.5 mmHg at all time points (Table 5). These data suggest that MONOPROST® is non-inferior to XALATAN™ at reducing IOP.

Table 5 – Comparison of Mean IOP (mmHg) by Time after 6 weeks of Treatment (Worst eye, Per Protocol Population) [LT2345-PII-10/07]

Time	IOP (Mean \pm SD) [mm Hg]			Mean Difference MONOPROST® minus XALATAN™ (Mean \pm SE) [mm Hg]	95% CI‡
	Baseline	MONOPROST® (% change)	XALATAN™ (% change)		
8 am	22.8 \pm 2.9	16.6 \pm 2.2 (-26%)	16.2 \pm 2.9 (-28%)	0.47 \pm 2.54	- 0.56, 1.49
12 pm	23.6 \pm 3.6	16.5 \pm 2.6 (-29%)	16.4 \pm 2.9 (-30%)	0.06 \pm 2.77	-1.06, 1.18
4 pm	22.6 \pm 3.7	15.9 \pm 3.0 (-28%)	16.4 \pm 3.0 (-26%)	-0.42 \pm 2.64	-1.49, 0.64
8 pm	21.9 \pm 4.4	16.3 \pm 3.3 (-24%)	16.6 \pm 3.2 (-23%)	-0.25 \pm 3.70	-1.74, 1.24
Diurnal	22.7 \pm 3.0	16.3 \pm 2.4 (-27%)	16.4 \pm 2.6 (-27%)	-0.04 \pm 2.10	-0.89, 0.81

‡ Non-inferiority margin of 1.5 mmHg. IOP: intraocular pressure; SD: standard deviation; 95% CI: 95% confidence interval.

Phase III - LT2345-PIII-12_08

Intraocular pressure (IOP) was measured in the worst eye at 9 am after 2 weeks, 6 weeks, and 3 months of treatment. Both treatments significantly lowered IOP compared to baseline with a 36% reduction for MONOPROST® and 38% reduction for XALATAN™. The upper limit of the 95% confidence interval for the estimated mean difference between MONOPROST® and XALATAN™ was lower than the non-inferiority margin of 1.5 mmHg at the 9 am time point after 2 weeks, 6 weeks, and 3 months of treatment (Table 6). After 6 weeks and 3 months of treatment, MONOPROST® was also non-inferior to XALATAN™ based on a more stringent non-inferiority margin of 1.0 mmHg. These data suggest that MONOPROST® is non-inferior to XALATAN™ at reducing IOP.

Table 6 - Comparison of Mean IOP (mmHg) Change from Baseline by Visit at 9 am Time point (Worst eye, Per Protocol Population) [LT2345-PIII-12_08]

Visit	MONOPROST®		XALATAN™		Mean Difference MONOPROST® minus XALATAN™ (Mean ± SE) [mm Hg]	95%CI‡
	N	Change in IOP (Mean ± SD) [mm Hg]	N	Change in IOP (Mean ± SD) [mm Hg]		
2 weeks	131	-8.5 ± 2.7	117	-9.0 ± 2.6	0.633 ± 0.291	0.060, 1.206
6 weeks	132	-9.0 ± 2.8	117	-9.4 ± 2.4	0.469 ± 2.58	-0.038, 0.976
3 months†	131	-8.9 ± 2.6	118	-9.3 ± 2.5	0.469 ± 0.254	-0.032, 0.970

Mixed effect model for repeated measures adjusted for baseline IOP, treatment, country, visit, treatment by visit interaction, and baseline IOP by visit interaction.

† Primary efficacy endpoint.

‡ Non-inferiority margin of 1.5 mmHg.

IOP: intraocular pressure; SD: standard deviation; SE: standard error of the mean; 95% CI: 95% confidence interval.

Supplementary Phase III – T-2345-001 [US]

The supplementary study in patients with a history of open-angle glaucoma or ocular hypertension currently treated with XALATAN™ demonstrate that MONOPROST® induces a diurnal reduction in IOP similar to that observed with XALATAN™. Intraocular pressure (IOP) was measured in the worst eye at 8 am, 10 am, and 4 pm after 2 weeks, 6 weeks, and 3 months of treatment. The upper limit of the 95% confidence interval for the estimated mean difference between MONOPROST® and XALATAN™ was lower than the non-inferiority margin of 1.5 mmHg at all (9/9) time points (i.e., 8 am, 10 am, and 4 pm after 2 weeks, 6 weeks, and 3 months treatment) (Table 7). Additionally, the upper limit of the 95% confidence interval of the estimated difference between MONOPROST® and XALATAN™ was lower than the more stringent non-inferiority margin of 1.0 mmHg at the majority (5/9) of time points. These data support the previous studies that suggest MONOPROST® is non-inferior to XALATAN™ at reducing IOP.

Table 7 - Comparison of Mean IOP (mmHg) by Time and Visit Treatment (Worst eye, Per Protocol Population) [T-2345-001 [US]]

Visit and Time	IOP (Mean ± SD) [mm Hg]		Mean Difference MONOPROST® minus XALATAN™ (Mean) [mm Hg]	95% CI‡
	MONOPROST®	XALATAN™		
2 weeks				
8 am	16.8 ± 3.2	16.1 ± 2.7	0.82	0.28, 1.36
10 am	15.9 ± 2.9	15.8 ± 2.9	0.42	-0.11, 0.94
4 pm	16.1 ± 2.8	16.1 ± 3.1	0.41	-0.12, 0.93
diurnal	16.3 ± 2.7	16.0 ± 2.5	0.57	0.15, 0.99
6 weeks				
8 am	16.7 ± 3.1	16.4 ± 2.9	0.30	-0.26, 0.85
10 am	15.8 ± 3.0	15.8 ± 2.9	0.27	-0.26, 0.81
4 pm	16.2 ± 2.9	15.9 ± 2.8	0.63	0.12, 1.15
diurnal	16.3 ± 2.7	16.1 ± 2.5	0.43	-0.02, 0.88
3 months				
8 am	16.7 ± 3.1	16.1 ± 2.6	0.69	0.15, 1.24
10 am	16.0 ± 2.9	15.9 ± 2.7	0.30	-0.17, 0.78
4 pm	16.4 ± 2.8	16.2 ± 3.0	0.57	0.05, 1.09
diurnal	16.3 ± 2.6	16.1 ± 2.4	0.52	0.11, 0.93

Safety results

No adverse events were identified with MONOPROST® that have not been well documented with XALATAN™. The most frequently elicited adverse events with MONOPROST® or XALATAN™ were “conjunctival hyperemia” and “instillation site pain” (see Table 1 and Table 2). MONOPROST® was associated with fewer subjective symptoms of burning/stinging upon instillation and irritation/burning/stinging not upon instillation compared to XALATAN™. These events, however, were predominantly reported as “present but not disturbing” suggesting that these symptoms have limited clinical meaningfulness. These findings are consistent with the body of data that shows that the presence of benzalkonium chloride (BAK) in ophthalmic solutions is known to induce ocular irritation, in particular when administration is repeated and prolonged.^{2,3,4}

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

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

Reduction of IOP – In the cat, topical administration of doses of 0.3-3 µg had limited IOP reducing effect. In the cynomolgus monkey, topical doses of 1-9.5µg caused a dose-dependent reduction in IOP. The onset of effect was relatively slow, with maximum reduction observed 4 to 6 hours after dosing. Repeated administration of 1-3 µg latanoprost once daily for five days, effectively lowered IOP.

Aqueous Humour dynamics: mode of action - The effect of latanoprost on aqueous humour dynamics was studied in cynomolgus monkeys. Topical administration of 3 µg latanoprost was applied once-daily for five days. On the fifth day of treatment, the aqueous humour dynamics was determined using iodine labelled albumin as tracer, while the 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 main mechanism for intraocular pressure reduction following latanoprost treatment, therefore, appears to be an increased uveoscleral outflow of aqueous humour. These results are in agreement with earlier studies with PGF_{2α}-IE demonstrating the same main mechanism to lower IOP.

Other pharmacologic effects in the eye - In the cat, latanoprost had a marked pupillary constrictive effect. Topical administration of 0.3-3 µg latanoprost caused a dose-dependent reduction of the pupillary diameter, with a maximum response observed 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 observed after latanoprost treatment. In human clinical studies, no change in pupil diameter has been observed during latanoprost treatment. The difference in miotic effect between species following latanoprost treatment may be attributed to the variation in prostaglandin receptors distribution.

Effects on airway resistance – In monkeys, 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 human 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 that latanoprost can cause a degree of constriction of the bronchial airway.

Cardiovascular and pulmonary effects - The effects of intravenously administered latanoprost on the cardiovascular and pulmonary system in unanesthetized cynomolgus monkeys have 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. Latanoprost did not contribute to a consistent effect on arterial blood pressure, but did cause a dose-related increase in heart rate in 2 out of 4 animals. Dose-related increases in respiration rate were recorded in all four animals following latanoprost treatment, with 500 µg/kg latanoprost causing a doubling in respiration rate. Animals showed no signs of dyspnea. No consistent dose-related changes in ECG could be detected, however, 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 human 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), the lowest dose corresponding to approximately 15 times the human clinical dose in the eye (~0.04 µg/kg). At the highest dose (150 times the human 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. Marked increases in blood flow were detected in the temporal, parietal, and frontal lobes of the brain with the highest dose of latanoprost.

Latanoprost caused a dose-related increase in coronary blood flow but limited effect on renal blood flow. Minor changes in blood flow were detected in most other organs.

Based on these data, topically administered latanoprost to the eye at clinically relevant doses is considered to have limited systemic effect on the cardiovascular system.

Human Pharmacodynamics

The active substance latanoprost, a prostaglandin F_{2α} analogue, is a selective prostanoid FP receptor agonist that reduces IOP. The mechanism of action of latanoprost is complex and not fully understood. Clinical and nonclinical studies suggest that the main mechanism of action is increased uveoscleral flow, with no significant effect on the production of aqueous humour. This mechanism of action is proposed in the human eye.⁵

A double-masked study was performed that included 20 healthy 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 placebo treated 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 cannot 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.

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.

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 hours in plasma. 88% is eliminated by the kidneys, essentially all of it within 24 hours, and 15% through faeces with a more prolonged elimination time indicating some biliary excretion of drug or metabolites (< 0.09% 144-168 hours 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.

The comparative pharmacokinetics of latanoprost from MONOPROST® and XALATAN™, respectively, were assessed in a phase II controlled clinical study conducted in 30 patients newly diagnosed with open-angle glaucoma or ocular hypertension. At each assessed time point (0, 5, 10, 15, and 30 min after instillation), the number of patients with values below the limit of quantitation (LOQ: 40.0 pg/mL) was similar between groups; except at 5 min after instillation, where 22 patients treated with XALATAN™ compared to 10 patients treated with MONOPROST® had values above the LOQ. C_{max} was determined to be lower following MONOPROST® than XALATAN™ instillation (52.7 pg/mL vs. 74.3 pg/mL; p=0.02). T_{max} was 10.7 min following MONOPROST® instillation and 7.3 min following XALATAN™ instillation. These data suggest MONOPROST® absorption is marginally slower than XALATAN™; however, this difference is not considered to be clinically relevant (see Table 3).

TOXICOLOGY

Toxicological studies performed in mice, rats, rabbits, dogs, and monkeys indicate that there is a relatively high therapeutic index with latanoprost with respect to systemic side effects. The maximum human 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. As a result 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 human 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 ingested dose was 50 mg/kg (approximately 1 million times the human clinical dose). No toxic symptoms were observed in an i.v. toxicity study in dogs, no mortality occurred at doses of 170, 340, or 680 µg/kg (approximately 150,000 to 600,000 times the human clinical dose). Clinical signs observed were similar to those reported after PGF_{2α}.

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 (12 months), cynomolgus monkeys (12 months), and rhesus monkeys (24 months).

Studies in Rabbits - Three ocular tolerance studies with twice daily administration were performed in rabbits for 28 days. The administration of MONOPROST® was well tolerated. One study compared MONOPROST® with XALATAN™ instilled into the eyes of pigmented rabbits. In the other two studies, the comparison was made between MONOPROST®, vehicle, a degraded MONOPROST® sample, and XALATAN™ in non-pigmented rabbits. Neither significant ocular effects nor clinical findings were observed.

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. 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 previously 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 previously 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. Similar to previous results, 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 previously. These consisted of a change in the aspect of the palpebral fissure (one male at 6 µg/eye/day) and an increase in the iris pigmentation in the majority of animals. With the lower doses of latanoprost, these 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 cynomolgus monkey: a dose-dependent reversible increase of the palpebral fissure (6 and 20 µg/day), and an 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_{2α} and PGE₂, 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. Similarly, latanoprost-induced increased iris pigmentation in sympathectomized rabbits was not 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. Furthermore, there was no uptake of 5-bromodeoxyuridine (5-BrU) or tritiated thymidine into melanocytes incubated with latanoprost acid, which strongly indicate that DNA synthesis 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, increasing the melanin content of the iridial melanocytes, with no observed proliferative changes occurring 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 5,000 times the human clinical dose) and the maximum dose in oil solutions was 10 mg/kg/day (approximately 250,000 times the human clinical dose). The studies in mice and rats were 28 days and 13 weeks, respectively. No toxic effects were observed.

Intravenous repeated dose administration - The studies were performed in rats and dogs and were of 4 and 13 weeks duration. In the 4 week study, rats were injected i with latanoprost at doses of 1, 10, 100, and 340 µg/kg/day. In the 13 week study in rats, rats were injected with latanoprost at doses of 5, 35, and 250 µg/kg/day. In the intravenous studies, mortalities occurred in rats given 250 µg/kg/day (approximately 5,000 times the human clinical dose). The mortalities were due to acute cardiovascular effects.

In the 4 week dose-finding study in the dog, latanoprost doses of 1, 10, 100, and 340 µg/kg/day were tested. Latanoprost 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 observed at the dose of 10 and 100 µg/kg/day, and vomiting at the dose of 100 µg/kg. No pathological changes were observed.

Reproduction and Teratology

To study the effect of latanoprost on fertility, teratology and both peri- and postnatal development, latanoprost has been administered intravenously to male and female rats before and during pregnancy. 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.

Fertility and 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 administered 10 µg/kg/day or more of latanoprost; this effect was particularly marked in the group administered 100 µg/kg/day of

latanoprost. The highest 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 selected dose levels (5, 50 and 250 µg/kg/day) of latanoprost. Latanoprost did, however, induce embryo-lethal effects in rabbits at doses above 5 µg/kg/day. The dose level of 5 µg/kg/day caused an 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, respectively. The effects on the foetal development are probably due to a pronounced luteolytic effect in the rabbit that has been described as a pharmacologic property of prostaglandin F_{2α} and its analogues.

The fetoplacental 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 detected. In the milk, the concentration of radioactive latanoprost was shown to be eliminated more slowly than for plasma. Of the radioactivity remaining in milk at 2 hours and 8 hours, 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* and *in vivo* methods.

The *in vitro* mutagenic potential was tested in bacteria (*Salmonella typhimurium* and *Escherichia 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.

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. 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. Owing to the favourable 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 at week 88, and the females at week 92. The dose levels (2, 20, and 200 µg/kg/day) were chosen based on the human clinical dose level and previous toxicity and pharmacokinetic studies. The highest dose was approximately 5,000 times the human clinical 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. The mean maximal plasma concentration of the acid of latanoprost 5 min after the last dose was about 50 times higher than the maximal human plasma concentration after a clinical dose in both eyes.

There were no clinical signs attributed 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 latanoprost. 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 latanoprost. 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 latanoprost. There were no unusual tumour types or increased incidence of tumours attributable to latanoprost. These data suggest that latanoprost has no carcinogenic potential in the mouse.

The design of the carcinogenicity study in rats was the same as in mice, but of a longer duration. The dose levels were based on the human clinical dose level and previous toxicity and pharmacokinetic studies. The highest dose of 200 µg/kg/day, was approximately 5,000 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.

There were no clinical signs attributed 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 with latanoprost. 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 latanoprost. There was no indication that red or white blood cell counts were affected by latanoprost. The spectrum of necropsy findings in latanoprost treated animals was generally similar to that in controls. There were no unusual non-neoplastic findings or increased incidence of tumours attributable to latanoprost. These data suggest that 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 latanoprost. These data suggest that latanoprost has no carcinogenic potential in the rat.

Special Toxicity

Three repeat-dose ocular tolerance studies were done in rabbits. MONOPROST®, vehicle, degraded MONOPROST®, and XALATAN™ were similarly well tolerated.

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

REFERENCES

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PART III: CONSUMER INFORMATION

IMPORTANT PLEASE READ

DINxxxxx

Pr **MONOPROST®**

Latanoprost ophthalmic solution
50 µg/mL

(Sterile, preservative free, single-dose container)

This leaflet is part III of a three-part "Product Monograph" published when MONOPROST was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MONOPROST. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MONOPROST is used to treat ocular hypertension (high pressure in the eye) in patients with open-angle glaucoma or ocular hypertension. These conditions may eventually affect your eyesight.

What it does:

MONOPROST is a preservative-free solution for use only in the eyes. The active ingredient in MONOPROST belongs to a group of medicines known as prostaglandins. It lowers the pressure within your eye by increasing the natural outflow of fluid from inside the eye.

When it should not be used:

Do not use MONOPROST:

- If you are allergic (hypersensitive) to latanoprost or any of the other ingredients of this medicine (see non-medicinal ingredients).

What the medicinal ingredient is:

Latanoprost.

What the important non-medicinal ingredients are:

Macrogolglycerol hydroxystearate 40, sorbitol, carbomer 974P, macrogol 4000, disodium edetate, sodium hydroxide (for pH-adjustment), water for injection.

What dosage forms it comes in:

MONOPROST is available in single-dose containers packed in a sachet of 5 units. A pack size contains 30 (6 x 5) or 90 (18 x 5) single-dose containers.

WARNINGS AND PRECAUTIONS

Talk to your doctor or pharmacist before using MONOPROST if you think any of the following apply to you:

- If you are about to have or have had eye surgery (including cataract surgery).
- If you suffer from eye problems (such eye pain, irritation or inflammation, blurred vision).
- If you have liver or kidney problems
- If you know that you suffer from dry eyes.

- If you have severe asthma or your asthma is not well controlled, or you have chronic obstructive pulmonary disease (COPD).
- If you suffer from eye problems such as eye pain, irritation, inflammation (e.g. uveitis, iritis) or blurred vision.
- If you wear contact lenses. You can still use MONOPROST, but follow the instruction for contact lens in PROPER USE OF THIS MEDICATION.
- If you have suffered or are currently suffering from a viral infection of the eye caused by the herpes simplex virus (HSV).

Children: MONOPROST has not been investigated in children (below 18 years) and is not recommended for use in children.

Pregnancy and breast-feeding: Ask your doctor for advice before using MONOPROST if you:

- are pregnant or plan to become pregnant
- are breast-feeding or plan to breast-feed

Driving and using machines: When you use MONOPROST you might have blurred vision, for a short time. If this happens to you, do not drive or use any tools or machines until your vision becomes clear again.

Important information about some of the ingredients: MONOPROST contains macrogolglycerol hydroxystearate (derived from castor oil) which may cause skin reactions.

INTERACTIONS WITH THIS MEDICATION

MONOPROST may interact with other medicines. Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Mixing other eye drops containing thiomersal with MONOPROST may result in precipitation (solids appearing) in the drops. If these drugs or other eye drops are used, allow at least 5 minutes between the application of each medicine.

Let your doctor know if you are taking other prostaglandin products.

PROPER USE OF THIS MEDICATION

Usual dose

- Always use MONOPROST exactly as your doctor has advised you, until your doctor tells you to stop. Check with your doctor or pharmacist if you are not sure.
- The usual adult dose (including the elderly) is one drop once a day in the affected eye(s). The best time to do this is in the evening.
- Do not use MONOPROST more than once a day, because the effectiveness of the treatment can be reduced if you administer it more often.

Contact lens wearers: If you wear contact lenses, you should remove them before using MONOPROST. After using MONOPROST you should wait 15 minutes before putting your contact lenses back in.

Instructions for use: The drops are supplied in single-dose containers. The solution from one individual single dose container of MONOPROST is to be used immediately after opening for administration to the affected eye(s). Since sterility cannot be maintained after the individual single dose container is opened, a new container must be opened prior to each use and must be discarded immediately after administration.

Please wash your hands then sit or stand comfortably before following these instructions to use the drops:

1. Open the container using your fingers from one hand to hold the body of the container. Using the fingers from the other hand hold the top of the container. With a snapping motion break the top off the container.
2. Use your finger to gently pull down the lower eyelid of your affected eye.



3. Place the tip of the single-dose container close to, but not touching your eye. Avoid contact between the container tip and the eye and eyelid.
4. Squeeze the single-dose container gently so that only one drop goes into your eye and then release the lower eyelid.
5. Press a finger against the corner of the affected eye by the nose. Hold for 1 minute whilst keeping the eye closed.



6. Repeat in your other eye if your doctor has told you to do this.
7. Discard the single-dose container after use. Do not keep it to use it again.

Contact your doctor or pharmacist as soon as possible if you swallow MONOPROST accidentally.

Using MONOPROST with other eye drops: Wait at least 5 minutes between using MONOPROST and using other eye drops.

If you stop using MONOPROST: You should speak to your doctor if you want to stop using MONOPROST.

If you have any further questions on the use of this medicine,

ask your doctor or pharmacist.

Overdose:

If you put too many drops into your eye, you may experience some minor irritation in your eye and your eyes may water and turn red, this should pass, but if you are worried contact your health care practitioner for advice.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use MONOPROST wait until it is time to take the next dose at the usual time. Do not take more than one dose. If you are unsure about anything talk to your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them.

MONOPROST may cause:

- A gradual change in your eye colour by increasing the amount of brown pigment in the coloured part of the eye known as the iris.
 - If you have mixed-colour eyes (blue-brown, grey-brown, yellow-brown or green-brown) you are more likely to see this change than if you have eyes of one colour (blue, grey, green or brown eyes).
 - Changes in eye colour may not noticeable for several months to years.
 - The colour change may be permanent and may be more noticeable if you use MONOPROST in only one eye.
 - This colour change is not known to be associated with any symptom of pathological change.
 - The eye colour change does not continue after MONOPROST treatment is stopped.
- Redness of the eye.
- Eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye).
- A gradual change to eyelashes of the treated eye and the fine hairs around the treated eye. These changes involve an increase of the colour (darkening), length, thickness and number of your eye lashes.

Common side effects in the eye:

- Burning, stinging, red eyes, eye pain, dry eyes, instillation pain/itching, excess tearing
- Feeling something is in the eye, blurred vision, sensitivity to light,
- Staining or damage to the surface of the cornea

Uncommon side effects in the eye:

- Double vision, eye discharge, conjunctivitis, eyelid inflammation
- Iritis or uveitis (inflammation of the interior of the eye)
- Inflammation of the cornea

Common side effects in the body:

- muscle and joint pain, bronchitis, sinusitis, skin rash

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any side effects not listed in this leaflet.

This is not a complete list of side effects. For any unexpected effects while taking MONOPROST, contact your doctor or pharmacist.

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 0701D
Ottawa, Ontario
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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Laboratoires THEA, 12 rue Louis Blériot 63017 Clermont-Ferrand Cedex 2 – FRANCE.

1-800-XXX-XXXX

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HOW TO STORE IT

Store MONOPROST between 15 and 25°C and protect from light.

Do not use this medicine after the expiry date which is stated on the carton, sachet and single-dose container.

After opening the sachet of 5 single-dose containers, use the containers within 7 days.

After first opening the single-dose container, use immediately and discard the single-dose container after use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

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