PT Pfizer Indonesia
Local Product Document

Generic Name	:	Latanoprost
Trade Name	:	Xalatan
CDS Effective Date	:	June 14, 2016
Supercedes	:	August 07, 2013

Special Warning and Special Precaution for Use:
Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since this drug contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

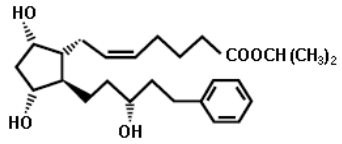
Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. This drug should not be used to treat contact lens related irritation. The preservative in this drug, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red** should be instructed to wait at least ten minutes after instilling this drug before they insert their contact lenses.

QUALITATIVE AND QUANTITATIVE COMPOSITION

	1 mL	One bottle with 2.5 mL
Latanoprost	50 micrograms	125 micrograms

One drop contains approximately 1.5 micrograms latanoprost.

The structural formula is represented below:



PHARMACEUTICAL FORM
Eye drops, solution

CLINICAL PARTICULARS
THERAPEUTICS INDICATIONS
Reduction of elevated intraocular pressure in patients with open angle glaucoma, chronic angle closure glaucoma and ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

POSOLOGY AND METHOD OF ADMINISTRATION
Recommended dosage for adults (including the elderly):
Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if Xalatan® is administered in the evening. If one dose is missed treatment should continue with the next dose as normal.

Administration:
Pivotal studies have demonstrated that Xalatan® is effective as a single drug therapy. Although definitive clinical trials of combination use have not been done a three-month study shows that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least party additive with cholinergic agonist (pilocarpine).

Xalatan® may be used concomitantly with other topical ophthalmic drug product to lower intraocular pressure. In case of combined therapy the eye drops should be administered with an interval of at least five minutes. The dosage of Xalatan® should not exceed once daily since it has been shown that more frequent administration decreases the intra ocular pressure lowering effect.

Children:
Safety and effectiveness in children has not been established. Therefore Xalatan® is not recommended for use in children.

CONTRAINDICATIONS
Known hypersensitivity to any component in Xalatan®. *In vitro* studies have shown that precipitation occurs when eye drops containing thiomerosal are mixed with Xalatan®. If such drugs are used, the eye drops shall be administered with an interval of at least five minutes.

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Iris pigmentation changes

Xalatan® may gradually change the eye colors by increasing the amount of brown pigment in 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, and is due to increased melanin content in the stromal melanocytes of the iris. A permanent heterochromia can happen. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. In patients with homogenously blue, grey, green or brown eyes, the change has only rarely seen during two years of treatment in clinical trials. The change in iris color occurs slowly and may not be noticeable for several months to years. It has not been associated with any symptom or pathological changes in clinical trials. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant color change may be permanent.

The potential for heterochromia exists for patients receiving unilateral treatment.

Until further long term data is obtained it is recommended that in patients with mixed colored irides only those who are intolerant or insufficiently responsive to another intraocular lowering medication be treated.

Neither nevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials, but until further long term experience about increased iris pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye color.

Glaucoma

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

Macular edema

Macular edema, including cystoid macular edema, has been reported during treatment with Xalatan®. 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 oedema. Xalatan® should be used with caution in these patients.

Xalatan® contains benzalkonium chloride which may be absorbed by contact lenses. The contact lenses should be removed before instillation of the eye drops and maybe reinserted after 15 minutes (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**). Xalatan® should not be administered while wearing contact lenses. Xalatan® has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Herpetic keratitis

Xalatan® should be used with caution in patients with a history of herpetic keratitis, and 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.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTIONS

The intraocular pressure reducing effect of latanoprost has been shown to be additive to that of beta-adrenergic antagonists (timolol), adrenergic agonists (dipivalyl epinephrine), carbonic anhydrase inhibitors (acetazolamide), and at least partly to cholinergic agonists (pilocarpine) in short term clinical trials.

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

PREGNANCY AND LACTATION

Fertility
Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section **Preclinical Safety Data** – *Impairment of Fertility* – **Latanoprost**).

Pregnancy
This medicinal product does not increase the spontaneous incidence of birth defects, but it has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or neonate.

Latanoprost has been shown to cause embryofetal toxicity in rabbits characterized by increase incidences of late resorption and abortion and reduced foetal weight when given in intravenous doses approximately 100 times the human dose.

Xalatan® should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section **Preclinical Safety Data** – *Impairment of Fertility*).

Lactation
The active substance in Xalatan® and its metabolites may pass into breast milk and Xalatan® should therefore be used with caution in nursing women.

EFFECTS ON ABILITY TO DRIVE AND USE OF MACHINES

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

UNDESIRABLE EFFECTS

ADRs by SOC and CIOMS frequency category (i.e., Very common, Common, Uncommon, Rare, and Very rare) and in order of decreasing medical seriousness within each frequency category and SOC.

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations				Herpetic keratitis*
Nervous system disorders		Dizziness*; headache*		
Eye disorders	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eye pain; eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes)*; ocular hyperaemia; iris hyperpigmentation; blepharitis; conjunctivitis*	Macular oedema including cystoid macular oedema*; photophobia*; eyelid oedema; keratitis*; uveitis*	Corneal oedema*; iritis*	Punctate keratitis*; corneal erosion*; trichiasis*; vision blurred*; periorbital and lid changes resulting in deepening of the eyelid sulcus*; darkening of the palpebral skin of the eyelids*; localised skin reaction on the eyelids*; iris cyst*; pseudopemphigoid of the ocular conjunctiva*
Cardiac disorders		Angina; palpitations*		Angina unstable*
Respiratory, thoracic and mediastinal disorders		Asthma*; dyspnoea*		Asthma aggravation*; acute asthma attacks*
Skin and subcutaneous tissue disorders		Rash	Pruritus	
Musculoskeletal and connective tissue disorders		Myalgia*; arthralgia*		
General disorders and administration site conditions		Chest pain*		

*ADR identified post-marketing

Adverse reactions reported with the use of eye drops containing phosphate buffers

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

Overdose

If overdosage with Xalatan® occurs, treatment should be symptomatic.

Apart from ocular irritation and conjunctival hyperemia no other ocular side effects are known if Xalatan® is overdosed.

If Xalatan® is accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolized during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating.

PHARMACOLOGY
Pharmacodynamic Properties

The active substance latanoprost, a prostaglandin F2α analogue, is a selective prostanoid FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humour. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in out-flow facility (decrease in out flow resistance) has been reported in man. Pivotal studies have demonstrated that XALATAN is effective as a single drug therapy. Although definitive clinical trials of combination use have not been done a three month study shows that latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibition (acetazolamide) and at least partly additive with cholinergic agonist (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour.
Latanoprost has not been found to have any effect on the blood-aqueous barrier.
Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

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

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

Latanoprost in clinical doses has not been found to have any significant pharmacologic effects on the cardiovascular or respiratory system.

Pharmacokinetic Properties
Absorption
Latanoprost (MW 432.58) is an isopropyl ester prodrug which per se is inactive but after hydrolysis to the acid of latanoprost becomes biologically active.
The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through cornea.
Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration.

Distribution
The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first four hours, and in plasma only during the first hour after local administration.

Metabolism
Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion
The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}$ =17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Preclinical safety data

Systemic/Ocular Effects

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. In monkeys, latanoprost has been infused intravenously in doses up to 500 micrograms/kg without major effects on the cardiovascular system. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanesthetized monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In the eye no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris color may be permanent or slowly reversible, see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**.

In chronic ocular toxicity studies administration of latanoprost 6 micrograms/eye/day has also been shown to induce palpebral fissure.

This effect is reversible and occur at doses above the clinical dose level. The effects has not been shown in humans.

Carcinogenesis

Carcinogenicity studies in mice and rats were negative.

Mutagenesis

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test.
Chromosome aberrations were observed *in vitro* with human lymphocytes. Similar effects were observed with prostaglandin F2α, a naturally occurring prostaglandin, and indicates that this is a class effect. Additional mutagenicity studies on *in vitro*/*in vivo* unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency. Carcinogenicity studies in mice and rats were negative.

Impairment of Fertility

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats no embryotoxicity was observed at intravenous doses (5,50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits in doses of 5 micrograms/kg/day and above. The dose of 5 µg/kg/day (approximately 100 times the clinical dose) caused significant embryofoetal toxicity characterized by increased incidence of late resorption and abortion and by reduced foetal weight.

Teratogenesis

No teratogenic potential has been detected

Special precautions for storage Store unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F).
Protect from light.
Once opened the container shall be used within 4 weeks and may be stored at room temperature up to 25°C.

Nature and contents of container

Bottle (5 mL), dropper applicator (dropper tip), screw cap, tamper evident overcap of polyethylene.
Each bottle contains 2.5 mL eye drop solution corresponding to approximately 80 drops of solution.

Instruction for use/handling

The tamper evident overcap should be removed before use.

Supply
Xalatan® Eye Drops 0.005%; Box, plastic bottle 2.5 mL
Reg No.: DKI0186101046A1

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Manufacturing Belgium NV/SA, Puurs, Belgium

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia