Prostaglandin $F_{2\alpha}$ analogue
For prescription use only

Latano Santen
(Latanoprost ophthalmic solution 0.005%w/v)

[CONTRAINDICATION]
Known hypersensitivity to latanoprost or any other component of the product.

[DESCRIPTION]

Brand name	Latano Santen
Active ingredient	Latanoprost
Content per mL	50 µg
Excipients	Polysorbate 80, sodium chloride, dibasic sodium phosphate hydrate, sodium dihydrogen phosphate dihydrate, benzalkonium chloride, sodium hydroxide, phosphoric acid and purified water
pH	6.5 - 6.9
Osmolar ratio	0.9 - 1.0
Description	Clear, colorless, sterile, aqueous ophthalmic solution

[INDICATIONS]

Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension. It may also be used for the reduction of elevated intraocular pressure as an adjunct medical therapy in patients with primary chronic angle closure glaucoma.

Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.

[DOSAGE AND ADMINISTRATION]

Instill one drop in the affected eye(s) once daily.

Optimal effect is obtained if latanoprost is administered in the evening.

The dosage of latanoprost should not exceed once daily since it has been shown that more frequent administration decreases the IOP lowering effect.

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

Latanoprost may be used concomitantly with other classes of topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after fifteen minutes

Paediatric population
Latanoprost eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants (less than 36 weeks gestational age). Data in the age group <1 year (4 patients) are limited (see section **Precautions for Use**).

[PRECAUTIONS FOR USE]

1. Careful Administration (This product should be administered with caution to the following patients)

1) Caution is recommended when using latanoprost in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.[It has been reported the treatment induces macular edema including cystoid macular edema, and worsening vision associated with it.]
2) Patients with bronchial asthma or a history thereof**.** There is no experience in patients with severe or brittle asthma. Such patients should therefore be treated with caution until there is sufficient experience. [The treatment may possibly exacerbate or induce asthmatic attack.(See the section "Precautions other than the above")]
3) Patients with endophthalmitis (iritis and uveitis) [IOP elevation has been reported.]
4) Patients who may be carriers of herpes viruses [Corneal herpes has been reported.] Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.
5) Pregnant and breast-feeding women [see the section "Use during Pregnancy or Lactation".]

2. Important Precautions

1) Latanoprost may gradually change the eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in heterochromia.
   This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, green-brown and yellow-brown. The highest incidence was found in patients with green-brown and yellow-brown irides. In patients with homogeneously blue eyes, no change has been observed and in patients with homogenously grey, green or brown eyes, the change has only rarely been seen. The onset of the change is usually within the first eight months of treatment, but may occur later in a small number of patients.
   The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in the number of melanocytes. 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. Patients who develop increased iris pigmentation should be examined regularly and, depending on the clinical situation, treatment may be stopped. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent. It has not been associated with any symptom or pathological changes in clinical trials of up to 48 months duration.(see the section "Clinically significant adverse reactions".)
   Naevi or freckles of the iris have not been affected by treatment.
   Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in long term clinical trials.
   In a clinical trial designed to assess iris pigmentation over five years, there was no evidence of adverse consequences due to increased pigmentation even when administration of latanoprost continued. These results are consistent with post-marketing clinical experience since 1996. In addition, IOP reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with latanoprost can be continued in patients who develop increased iris pigmentation. These patients should be examined regularly and, depending on the clinical situation, treatment may be stopped.
   Onset of increased iris pigmentation typically occurs within the first year of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable by five years. The effects of increased pigmentation beyond five years have not been evaluated. 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.
2) During the administration of this product, corneal epithelial disorders (superficial punctate keratitis, filamentous keratitis and corneal erosion) may occur. In the case that subjective symptoms such as stinging, itching and eye pain continue, the patient should be fully instructed to seek immediate medical consultation.
3) There is limited experience with latanoprost in the chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of latanoprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Latanoprost has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that latanoprost should be used with caution in these conditions until more experience is obtained.
4) There are limited study data on the use of latanoprost during the peri-operative period of cataract surgery. Latanoprost should be used with caution in these patients.
5) Because temporary blurred vision may occur after using this drug, the patient should be advised not to drive or operate machines until the said symptom disappears.
6) Eyelid and eyelash changes
   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 include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.
Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.

7) In patients with known predisposing risk factors for iritis/uveitis, latanoprost should be used with caution.
8) Paediatric population
Efficacy and safety data in the age group <1 year (4 patients) are very limited (see section "Pharmacodynamic properties"). No data are available for preterm infants (less than 36 weeks gestational age).
In children from 0 to <3 years old that mainly suffers from PCG (Primary Congenital Glaucoma), surgery (e.g., trabeculotomy/goniotomy) remains the first line treatment. Long-term safety in children has not yet been established.

3. Drug Interactions

Precautions for coadministration (This drug should be administered with caution when administered with the following drugs.)

Drug name	Clinical symptoms / Measures	Action mechanism / Risk factor
Prostaglandin ophthalmic solutions such as: Isopropyl unoprostone and bimatoprost	IOP elevation has been reported.	Action mechanism unknown

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.

Paediatric population
Interaction studies have only been performed in adults.

4. Adverse Reactions

1) Clinically significant adverse reactions

Iris pigmentation: Because iris pigmentaion may occur, the patient should be examined periodically. If iris pigmentation appear, the treatment should be discontineud depending on the clinical status. (See the section "Important Precautions".)

2) Adverse reactions other than the above

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)
Eye disorders	Conjunctival hyperemia; conjunctivitis; eyelid pigmentation; blepharitis; eyelid hirsutism; ocular irritation such as stinging, eye itching; eye pain; abnormal changes of eyelashes (increased, thickended, lengthened); ocular discomfort such as foreign body sensation	Uveitis; filamentous keratitis; herpetic keratitis; keratic precipitates; corneal opacity; ulcerative keratitis; eyelid oedema; macular edema including cystoid macular edema and worsening vision associated with it; photophobia	Iritis; corneal oedema	eye discharge; conjunctival follicle; ocular pseudopemphigoid; iris cyst; superficial punctate keratitis; corneal erosion; eyelid redness; deepening of the eyelid sulcus; vision blurred
Cardiac disorders		Palpitations; angina pectoris		
Respiratory, thoracic and mediastinal disorders		Asthma		
Skin and subcutaneous tissue disorders		Rash; itching		
Musculoskeletal and connective tissue disorders		Muscle pain; arthralgia;		
General disorders and administration site conditions		Chest pain		
Nervous system disorders		Dizziness; headache		

Adverse reactions reported with the use of eyedrops 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.

Paediatric population

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

5. Use in the elderly

Because physiological function is generally reduced in the elderly, caution should be exercised.

6. Use during Pregnancy or Lactation

1) Pregnant women: There are no adequate and well-controlled studies in pregnant women. This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits are judged to outweigh the possible risks associated with the treatment. [The safety of this drug during pregnancy has not been established. A study on administration during the period of organogenesis in an animal (pregrant rabbits) revealed increased incidence of abortion and late fetal resorption and reduced fetal body weight by intravenous injection at approximately 80 folds of the clinical dose (5.0 μg/kg/day).]

2) Breast-feeding women: Latanoprost and its metabolites may pass into breast milk. Latanoprost should therefore be used with caution in nursing women. [In an animal study (intravenous injection to rats), latanoprost has been reported to be excreted into breast milk.]
3) Latanoprost has not been found to have any effect on male or female fertility in animal studies.

7. Paediatric Use

Efficacy and safety data in the age group <1 year (4 patients) are very limited (see section "Pharmacodynamic properties"). No data are available for preterm infants (less than 36 weeks gestational age).
In children from 0 to <3 years old that mainly suffers from PCG (Primary Congenital Glaucoma), surgery (e.g., trabeculotomy/goniotomy) remains the first line treatment.
Long-term safety in children has not yet been established.

8. **Overdose**

If overdosage with latanoprost occurs, treatment should be symptomatic.
Apart from ocular irritation and conjunctival hyperaemia, no other ocular adverse effects are known if latanoprost is overdosed.
If latanoprost is accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 mcg/kg in healthy volunteers induced no symptoms, but a dose of 5.5 - 10 mcg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost (see Preclinical safety data).

9. Precautions concerning Use

1)Route of administration: Ophthalmic use only.
2)At the time when this product is given to patients, they are instructed to:
(1) Be careful not to touch the tip of the bottle to the eye directly.
(2) Immediately wipe away any drops on the eyelid or the face if they spill out of the eye.
(3) If more than one topical ophthalmic drug is being used, at least five minutes of intervals should be taken.
(4) Benzalkonium chloride may change the color of the contact lenses. Contact lense wearers should remove the lenses before using this product and put them back 15 minutes or longer afterwards.

10. Preacautions other than the above

1) Overseas studies have reported retinal artery occulsion; retinal detachment; and vitreous hemorrhage associated with diabetic retinopathy as ocular topical adverse events, and upper respiratory tract infection; common cold; influenza; muscle pain; joint pain; lower back pain; chest pain; angina pectoris; rash; and allergic dermal reaction as systemic adverse events.
2) Intravenous administration of latanoprost (2 μg/kg) to monkeys induced transient airway resistance. It was reported, however, that there was no impact on 11 patients with moderate bronchial asthma when latanoprost at 7-fold higher than that of the clinical dosing (1.5 μg/eye) was instilled into their eyes.

[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. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In monkeys, latanoprost has been infused intravenously in doses of up to 500 mcg/kg without major effects on the cardiovascular system. In animal studies, latanoprost has not been found to have sensitizing properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

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 $F_{2\alpha}$, a naturally occurring prostaglandin, and indicate 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.

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 at doses of 5 micrograms/kg/day and above. Latanoprost has been shown to cause embryofetal toxicity in rabbits characterised by increased incidences of late resorption and abortion and reduced fetal weight when given in intravenous doses approximately 100 times the human dose.

Teratogenesis
No teratogenic potential has been detected.

[PHARMACODYNAMIC PROPERTIES]

The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour, primarily through the uveoscleral route and also through the trabecular meshwork. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.

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

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

Clinical studies of latanoprost in primary chronic angle closure glaucoma have been limited to 12 weeks. Clinical efficacy and safety in patients with primary chronic angle glaucoma have not been established beyond 12 weeks.

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

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

Paediatric population
The efficacy of latanoprost in paediatric patients ≤18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 0.005% once daily or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in IOP from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to <3 years, 3 to <12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 to <3 years were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 to <1 year old in the clinical paediatric study. No data are available for preterm infants (less than 36 weeks gestational age).

IOP reductions among subjects in the primary congenital/infantile glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup.

The effect on IOP was seen after the first week of treatment and was maintained throughout the 12-week period of study, as in adults.

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

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

SE: standard error
*: Adjusted estimate based on analysis of covariance (ANCOVA) model

[PHARMACOKINETIC PROPERTIES]

Absorption
Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolysed to the acid form to become biologically active. 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 humour during the first four hours, and in plasma only during the first hour after local administration.

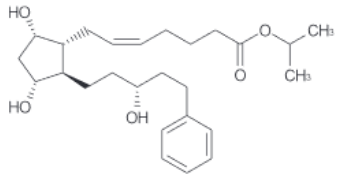
Metabolism
Latanoprost, an isopropyl ester prodrug, is hydrolysed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolised by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

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.

Paediatric population
An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (from birth to <18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 0.005%, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to <12 year olds and 6-fold higher in children <3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained (see section 8). Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (<20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

[PHYSICOCHEMISTRY]
Nonproprietary name: Latanoprost
Chemical name: (+)-Isopropyl (*Z*)-7-[(1*R*, 2 *R*, 3*R*, 5S)-3, 5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate

Structural formula:



Molecular formula:
$C_{26}H_{40}O_5$
Molecular weight:
432.59
Description:
Latanoprost occurs as a colorless to yellow viscous liquid. It is freely soluble in acetonitrile, methanol, ethanol (99.5) or ethyl acetate, and practicaly insoluble in hexane or water.

[STORAGE]
Store at 2 to 8°C in a tight container.
Once a bottle is opened, it can be stored below 30°C for 31 days (one month).
Expiration date : Indicated on the package and label. (3 years)

[PACKAGING]
5 mL polyethylene bottle, a polyethylene dropper tip and a polypropylene cap.
Manufactured by:
Santen Pharmaceutical Co., Ltd.
Noto plant: 2-14, Shikinami, Hodatsushimizu-cho, Hakui-gun, Ishikawa, Japan

Revision date: Mar 2023

Approved 12-Apr-2023 22-49 UTC

Username	Full Name	Status	Date/Time (UTC)
JenniferRamirez	Jennifer Ramirez	Approved	08-Apr-2023 12-15 UTC
JacquelineWong	Jacqueline Wong	Approved	12-Apr-2023 06-28 UTC
KazuhiroNishino	Kazuhiro Nishino	Approved	12-Apr-2023 22-49 UTC