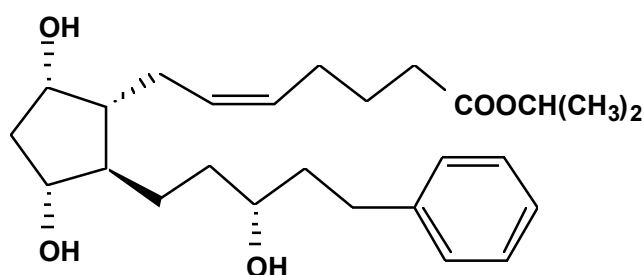


DATA SHEET

HYSITE[®], Eye Drops (Latanoprost 50 micrograms/mL)

NAME OF THE DRUG

latanoprost



The chemical name of latanoprost is Isopropyl-(Z)-7[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenyl-1-pentyl]cyclopentyl]-5-heptenoate, according to IUPAC.

DESCRIPTION

The active ingredient in HYSITE is latanoprost, a prostaglandin F_{2α} analogue. Latanoprost is a viscous oil which is practically insoluble in water, freely soluble in ethanol, ethyl acetate, isopropanol, methanol, acetone and octanol, and very soluble in acetonitrile.

Sixty four isomers of latanoprost are possible, however, for HYSITE it is purified as a single isomer.

HYSITE Eye Drops is a sterile, isotonic solution containing 50 micrograms/mL of latanoprost in an aqueous buffer solution of pH 6.7. The excipients in HYSITE are sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate anhydrous, water for injections and benzalkonium chloride (0.20mg/mL) as a preservative agent.

The solution is a clear and colourless liquid, filled in a polyethylene container.

PHARMACOLOGY

Pharmacokinetics

Latanoprost is an isopropyl ester pro drug which is inactive, but after hydrolysis to the acid of latanoprost, becomes biologically active.

The pro drug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration. After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eye lids. Only minute quantities of the drug reach the posterior segment.

Following an ocular dose of latanoprost, 45% of latanoprost acid is absorbed systemically, with 90% being bound to plasma proteins.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. Following intravenous administration in man, the half life in plasma is 17 minutes.

The main metabolites, the 1,2-dinor and 1, 2, 3, 4- tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Pharmacodynamics

Latanoprost, a selective prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

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 human clinical dose, as studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

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

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

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

CLINICAL TRIALS

Efficacy

In three pivotal, randomised, double blind, parallel group trials latanoprost 50µg/mL once a day was compared with timolol 5mg/mL twice a day. Across the three trials, 460 patients received latanoprost and 369 received timolol. At 6 months latanoprost reduced intraocular pressure (IOP) by 27 - 34% from the untreated baseline of 24.4 - 25.2mmHg and timolol reduced IOP by 20 - 33% from a baseline of 24.1 - 25.4mmHg. In one of these three studies, the difference between the reduction in IOP by latanoprost versus timolol was statistically significant ($p < 0.001$). A meta-analysis of the three trials demonstrated that of the intention-to-treat population, 61% of latanoprost treated patients, compared with 40% of timolol treated patients, reached a 30% reduction in diurnal IOP after 6 months. No tolerance to the effect of latanoprost was seen after 12 months in these trials.

The pivotal studies have demonstrated that HYSITE is effective as monotherapy. In addition, HYSITE is effective as adjunctive therapy in reduction of IOP. Short term (1 or 2 week) studies suggest the effect of latanoprost is additive in combination with adrenergic agonists (dipivefrine hydrochloride), carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine). Although intended primarily as a safety study, IOP reduction was effectively maintained over 48 months in a clinical trial of 356 patients receiving latanoprost as adjunctive therapy to various medications including β -adrenergic antagonists, adrenergic agonists, cholinergic agonists and carbonic anhydrase inhibitors. Out of 519 patients at study start, only 7 patients were withdrawn from the study due to uncontrolled IOP.

Clinical trials involving a fixed combination of latanoprost 50 µg/mL and timolol 5mg/mL given once daily have also been conducted. The mean diurnal IOP-lowering effect of the combination was greater than that produced by monotherapy with either latanoprost 50 µg/mL once daily or timolol 5mg/mL bd.

Safety

Long term safety of latanoprost has been investigated in an open label, multicentre, safety study. This trial enrolled 519 patients, 356 of whom continued for 48 months. Iris pigmentation changes have been observed in patients of the pivotal clinical trials of latanoprost (see also **PRECAUTIONS** and **ADVERSE EFFECTS**). The long term safety study has shown that this change is not associated with any increased risk of clinically significant ocular or systemic effects, nor is it considered to have any long term consequences.

In those patients experiencing colour change, the time to onset of increased iris pigmentation usually occurred within 8 months of starting treatment. Within 24 months, onset had occurred in almost all of these cases. Onset after 36 months of treatment was very rare. Using iris photography, the increase in iris pigmentation was graded as “weak” in 75 out of 124 patients (60.5%) during the first year of onset. A

weak grading was maintained in 42 of these patients (33.9%) over 48 months of treatment. In those patients showing iris pigmentation progression, there was no apparent increase in iris pigmentation during the fourth year of treatment, indicating a plateau in pigmentation had been reached. A separate safety study has also shown that reintroduction of latanoprost to patients with increased iris pigmentation will not necessarily lead to a further increase in iris pigmentation severity.

IOP reduction between patients who developed iris pigmentation, and those who did not, was shown to be comparable over 48 months. Table 1 below shows the mean IOP and change from baseline in patients experiencing increased iris pigmentation (IIP) and those not experiencing increased iris pigmentation (NIIP).

Table 1: IOP (mmHg) and change from baseline to 36 and 48 months' visits in relation to the absence (NIIP) or presence of increased iris pigmentation (IIP)

	Baseline	Month 36		Month 48	
	IOP	IOP	Δ IOP	IOP	Δ IOP
NIIP					
Mean	23.7	17.6	-6.1	18.2	-5.6
SD	4.7	3.8	4.2	4.4	4.7
n	263	263	263	246	246
IIP					
Mean	23.9	17.2	-6.7	17.3	-6.5
SD	3.9	3.5	4.2	3.6	4.9
n	117	117	117	110	110
All					
Mean	23.8	17.5	-6.3	17.9	-5.9
SD	4.4	3.7	4.2	4.2	4.8
n	380	380	380	356	356

INDICATIONS

Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Known hypersensitivity to any component in HYSITE.

PRECAUTIONS

WARNING: HYSITE may gradually change 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 colour irides i.e. blue-brown, grey-brown, green-brown or 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 homogeneously 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 (see **PHARMACOLOGY - Clinical Trials**).

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.

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.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of HYSITE.

HYSITE 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.

Use with caution in the following circumstances:

- Macular oedema, including cystoid macular oedema, has been reported uncommonly during treatment with HYSITE. These reports have mainly occurred in patients with aphakia or pseudophakia with anterior chamber lenses and/or torn posterior lens capsule, or in patients with known risk factors for macular oedema. Caution is recommended when using HYSITE in these patients. Upon discontinuation of HYSITE treatment, visual acuity has improved, in some cases with concurrent treatment with topical steroidal and non-steroidal anti-inflammatory drugs.

- There is no experience with HYSITE in inflammatory and neovascular glaucoma, inflammatory ocular conditions or congenital glaucoma. There is limited experience with HYSITE in chronic angle closure glaucoma (one 12 week study), open angle glaucoma of pseudophakic patients (4 out of 519 patients enrolled in the long term safety study were pseudophakic patients) and in pigmentary glaucoma (one 12 month study). HYSITE has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. HYSITE should be used with caution in these conditions until more experience is obtained.
- Use with contact lenses. HYSITE contains benzalkonium chloride which may be absorbed by contact lenses. The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.
- There is no experience in patients with severe or brittle asthma. Such patients should therefore be treated with caution until there is sufficient experience (see **ADVERSE EFFECTS**).
- Use with caution in patients with a history of herpetic keratitis, it 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.*

Animal toxicity

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Intravenous acute toxicity studies (2mg/kg) and oral acute toxicity studies (50mg/kg) in rats and mice resulted in no mortality. Latanoprost, 2-6 micrograms/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration.

In animal studies latanoprost has not been found to have sensitising properties.

In the eye no significant toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost at 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.

Carcinogenicity, Mutagenicity and Impaired Fertility

Latanoprost was not carcinogenic in either rats or mice when administered by oral gavage at doses up to 170µg/kg/day for 24 and 20 months respectively.

Latanoprost was not mutagenic in gene mutation assays in bacteria and mouse lymphoma L5178Y cells and was negative in studies of unscheduled DNA synthesis. Chromosome aberrations were observed with human lymphocytes in vitro but latanoprost did not induce micronucleus formation in vivo.

Latanoprost had no effect on male or female fertility studies in rats when administered intravenously with 250µg/kg.

Use in pregnancy (category B3)

The safety of HYSITE (latanoprost) for use in human pregnancy has not been established. Reproductive studies have been performed in rats and rabbits and no malformations or structural variations were observed in the fetuses at any doses of latanoprost. In rabbits given latanoprost IV at 5µg/kg/day, a slight increase of litter resorption occurred and at doses of 50 or 300µg/kg/day, total litter resorption (100%) in all animals was recorded. A dose of 1µg/kg/day was well tolerated in rabbits.

In pregnant rats dosed with tritium labelled latanoprost intravenously, the radioactivity was detected in all maternal tissues, placenta and foetus.

HYSITE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

There are limited experimental animal and no human data available on the pharmacokinetics of HYSITE in lactation. The active substance in HYSITE and its metabolites may pass into breast milk and HYSITE should therefore be used with caution in nursing women.

The benefits of treatment with HYSITE should clearly outweigh the possible risks for use in nursing mothers.

Paediatric Use

HYSITE is not recommended for use in children. Use in children has not been studied.

Interactions with other Medicines

Interactions with other medications other than those described in the **PHARMACOLOGY – Clinical Trials** section have not been investigated.

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

Incompatibilities: *In vitro* studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with HYSITE. If such drugs are used the eye drops should be administered with an interval of at least five minutes.

Effects on ability to drive and use of machines: In common with other eye preparations, installation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

ADVERSE EFFECTS

Short term treatment: Adverse events occurring at a frequency of >1% in 6 month comparative trials are presented in Table 2 below:

Table 2

Adverse events reported for latanoprost (>1%) in three pivotal 6 month, randomised, double blind trials comparing latanoprost 50 µg/mL once a day with timolol 5mg/mL twice a day.

Adverse event	Latanoprost (n= 460)	Timolol (n=369)
Ocular		
Blurred vision	2%	1.1%
Burning	2.8%	1.6%
Conjunctivitis	1.1%	3.0%
Excessive tearing	1.1%	0.3%
Eye pain	1.1%	0.3%
Foreign body sensation	2.8%	1.4%
Hyperaemia	5.7%	2.4%
Iris hyperpigmentation	1.7%	0%
Itching	2.0%	0.8%
Punctate epithelial erosions	4.3%	1.4%
Pulmonary		
Bronchitis	1.1%	1.6%
Upper respiratory tract infection	4.1%	4.1%
Dermatological		
Eczema	1.3%	1.6%
Rash	1.5%	0%
Urinary Tract		
Infection	1.1%	1.1%
Laboratory Values		
Abnormal liver function	1.1%	0.8%
(See also PRECAUTIONS)		

Chronic treatment (> 6 months)

Most of the adverse events observed relate to the ocular system.

Very common (>10% patients)

Ocular: Increased iris pigmentation; eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (darkening, thickening, lengthening, increased number).

Common (1 –10% patients)

Ocular: Mild to moderate conjunctival hyperaemia; transient punctate epithelial erosions, mostly without symptoms; blepharitis; eye pain; conjunctivitis; vision blurred; eyelid oedema

Musculoskeletal and Connective Tissue Disorders: Muscle/joint pain

Nervous System Disorders: Dizziness; headache

Skin and subcutaneous tissue disorders: localised skin reaction on the eyelids; skin rash

Uncommon (< 1% patients)

Ocular: Iritis/uveitis; keratitis; macular oedema including cystoid macular oedema

General Disorders and Administration Site Conditions: Non-specific chest pain

Respiratory, Thoracic and Mediastinal Disorders: Asthma; Dyspnoea

Rare (< 0.1% patients)

Ocular: Symptomatic corneal oedema and erosions; periorbital oedema; darkening of the palpebral skin; misdirected eyelashes sometimes resulting in eye irritation

Respiratory, Thoracic and Mediastinal Disorders: Asthma aggravation; acute asthma attacks

HYSITE may cause an increase in brown pigmentation of the iris, predominantly in patients with mixed coloured irides, (i.e. blue-brown, grey-brown, green-brown, yellow-brown). This is due to increased melanin content in the stromal melanocytes of the iris (see **PRECAUTIONS**).

Macular oedema has been reported uncommonly during HYSITE treatment. These reports have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lens, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion).

An association between the use of HYSITE and unexplained macular oedema cannot be excluded (see **PRECAUTIONS**).

Cases of iritis/uveitis have been uncommonly reported. The majority of patients in these cases had concomitant predisposing factors for developing iritis/uveitis.

Cases of asthma and dyspnoea have been uncommonly reported. Rare cases of asthma aggravation and acute asthma attacks have also been reported. There is limited experience from patients with asthma, but latanoprost has not been found to affect the pulmonary function when studied in a small number of steroid and non-steroid treated patients suffering from moderate asthma. There is no experience in patients with severe or brittle asthma and such patients should therefore be treated with caution until there is sufficient experience.

Herpetic keratitis, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus, have been reported.*

DOSAGE AND 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 HYSITE is administered in the evening. Systemic absorption can be minimised by pressure on the tear duct immediately after application of the eye drop.

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

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

Administration

HYSITE is effective as a single drug therapy but can also be used in combination with beta-adrenergic antagonists (timolol), adrenergic agonists (dipivefrine hydrochloride), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide) to achieve an additive effect. In case of combined therapy the eye drop products should be administered with an interval of at least five minutes.

Use with contact lenses: The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see **PRECAUTIONS**).

OVERDOSE

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

If HYSITE 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 micrograms/kg in healthy volunteers induced no symptoms but a dose of 5.5 - 10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with bronchial asthma bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of HYSITE.

If overdosage with HYSITE occurs, treatment should be symptomatic.

PRESENTATION AND STORAGE CONDITIONS

Each 5mL bottle contains 2.5mL eye drop solution corresponding to a minimum of 80 drops of solution. One drop contains approximately 1.5 micrograms latanoprost.

Store at 2° to 8° C.

Store opened bottle below 25°C. Store in the outer cardboard carton. To be used within 4 weeks after opening.

Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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* Please note changes in Data Sheet

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