SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MONOPOST 50 micrograms/ml eye drops, solution in single-dose container.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops solution contains 50 micrograms of latanoprost.

One drop contains approximately 1.5 micrograms of latanoprost.

Excipient with known effect: 1 ml eye drops solution contains 50 mg of macrogolglycerol hydroxystearate 40 (castor oil polyoxyl hydrogenated).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container.

The solution is a slightly yellow and opalescent solution.

pH: 6.5 – 7.5

Osmolality: 250-310mosmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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 MONOPOST is administered in the evening.

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

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

Paediatric population:

No data are available with MONOPOST formulation.

Method of administration

Ocular use.

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 should be performed immediately following the instillation of each drop.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least five minutes apart.

A single-dose contains enough eye drops solution to treat both eyes.

For single use only.

This medicinal product is a sterile solution that does not contain a preservative. The solution from one individual single dose container 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, any remaining contents must be discarded immediately after administration.

Patients should be instructed:

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Latanoprost 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 permanent heterochromia.

This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the onset of the change is usually within the first 8 months 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 for five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.8). The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the

highest incidence. 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 colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in 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. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Neither naevi 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. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, latanoprost treatment may be discontinued.

There is limited experience of latanoprost in 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, inflammatory ocular conditions, or congenital glaucoma. 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.

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.

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 history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Reports of macular oedema have occurred (see section 4.8) mainly 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 (such as diabetic retinopathy and retinal vein occlusion). Latanoprost should be used with caution 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.

In patients with known predisposing risk factors for iritis/uveitis, latanoprost can be used with caution.

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience, see also section 4.8.

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.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation,

number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

MONOPOST contains macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated) which may cause skin reactions. No long-term safety data are currently available on this excipient.

4.5 Interaction with other medicinal products and other forms of interaction

Definitive drug interaction data are not available.

There have been reports of paradoxical elevations in intraocular pressure 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.

4.6 Fertility, pregnancy and lactation

Fertility
Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section 5.3).

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, MONOPOST should not be used during pregnancy.

Breastfeeding
Latanoprost and its metabolites may pass into breast milk and MONOPOST should therefore not be used in breast-feeding women or breast feeding should be stopped.

4.7 Effects on ability to drive and use machines

No studies on the effect of this medicinal product on the ability to drive have been conducted. In common with other eye preparations, instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile
The majority of adverse events relate to the ocular system. In an open 5-year latanoprost reference product safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse events are generally transient and occur on dose administration.

b. Tabulated list of adverse reactions

The adverse events and their frequencies listed herebelow are those described for the reference product. Adverse events are categorized by frequency as follows: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,0000 to <1/1,000) and very rare (<1/10,000). Frequency not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,0000 to <1/1,000**	**Very Rare <1/10,000**
Infections and infestations				Herpetic keratitis*§	
Nervous system disorders			Headache*; dizziness*		
Eye disorders	Iris hyperpigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes)	Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis*	Eyelid oedema; dry eye; keratitis*; vision blurred; macular oedema including cystoid macular oedema*; uveitis*	Iritis*; corneal oedema*; corneal erosion; periorbital oedema; trichiasis*; distichiasis; iris cyst*§; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids	Periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders			Angina; palpitations*		Angina unstable
Respiratory, thoracic and mediastinal disorders			Asthma*; dyspnoea*	Asthma exacerbation	
Gastrointestinal disorders			Nausea*; vomiting*		
Skin and subcutaneous tissue			Rash	Pruritus	

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,0000 to <1/1,000	Very Rare <1/10,000
disorders					
Musculoskeletal and connective tissue disorders			Myalgia*; arthralgia*		
General disorders and administration site conditions			Chest pain*		

*ADR identified post-marketing
§ADR frequency estimated using "The Rule of 3"

c. Description of selected adverse reactions
No information is provided.

d.Paediatric population
No data are available with Monopost formulation

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

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

If MONOPOST is accidentally ingested the following information may be useful: One single-dose container contains 10 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and 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 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 MONOPOST.

If overdose with MONOPOST occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIGLAUCOMA PREPARATIONS AND MIOTICS; Prostaglandin analogues, ATC code: S01EE01.

Mechanism of action:

The active substance latanoprost, a prostaglandin $F_{2\alpha}$analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour.

Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Pharmacodynamic effects:

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 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.

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 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 system.

Clinical efficacy and safety

MONOPOST was evaluated in a three-month, randomised, investigator-masked study comparing non-preserved MONOPOST with the preserved 0.005% latanoprost reference product in 404 ocular hypertensive or glaucomatous patients. The primary efficacy variable was the change in intraocular pressure between baseline and Day 84.

At Day 84, the intraocular pressure reduction induced by MONOPOST was -8.6 mmHg i.e -36%. It was similar to that of the preserved 0.005% latanoprost reference product.

Worse eye (mITT population)		**MONOPOST**	**Reference Product**
Baseline (D0)	n	189	164
	Mean ± SD	24.1 ± 1.8	24.0 ± 1.7
D84	n	185	162
	Mean ± SD	15.4 ± 2.3	15.0 ± 2.0
Mean change (D0 – D84)	n	185	162
	Mean ± SD	**-8.6 ± 2.6**	**-9.0 ± 2.4**
	[95% CI]	[-9.0 ; -8.3]	[-9.4 ; -8.7]
Statistical analysis	E (SE)	**0.417 ± 0.215**	
	[95%CI]	**[-0.006; 0.840]**	

This three-month trial showed the following undesirable effects for MONOPOST and the latanoprost reference product respectively: irritation/burning/stinging not upon instillation (at D84, 6.8% for MONOPOST and 12.9 % for latanoprost reference product) and conjunctival hyperaemia (at D84, 21.4% for MONOPOST and 29.1% for latanoprost reference product). Concerning systemic adverse events, no major difference is observed between the two treatment groups.

5.2 Pharmacokinetic properties

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.

Absorption:

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

Distribution:

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 eyelids. Only minute quantities of the drug reach the posterior segment.

In a three-month, cross-over, randomised, pilot study in 30 hypertensive or glaucomatous patients, the latanoprost plasma level was measured and 30 minutes after instillation almost all patients had values which went down below the LOQ (40 pg/ml).

Biotransformation and Elimination:

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

5.3 Preclinical safety data

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 animal studies, latanoprost has not been found to have sensitising 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). 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 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.

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.

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.

The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant embryofoetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight.

No teratogenic potential has been detected.

Ocular toxicity

Ocular administration of MONOPOST eye drops to animals twice a day during 28 days did not demonstrate any local or systemic toxic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate 40

Sorbitol

Carbomer 974P

Macrogol 4000

Disodium edetate

Sodium hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in the outer packaging.

After first opening of the sachet, use the single-dose containers within 10 days.

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

6.4 Special precautions for storage

Store below 25°C.

For storage after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 or 10 single-dose containers (LDPE) containing 0.2 ml of eye drops solution are packed in sachet (copolymers/aluminium/polyethylene/paper or PE/aluminium/polyethylene/PET).

A pack size contains 5 (1x5), 10 (2x5), 10 (1x10), 30 (6x5), 30 (3x10), 90 (18x5) or 90 (9x10) single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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France

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