SUMMARY OF PRODUCT CHARACTERISTICS

BRUSCHETTINI S.r.l. – Genova (Italy)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT. Latanostill 50 µg/ml eye-drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION. 100 ml of eye-drops solution contains:
latanoprost 0.005 g.
One drop contains approximately 1.5 µg of latanoprost
Excipient: benzalkonium chloride 0.2% as preservative.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM. Eye drops, solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latanoprost is indicated for the reduction of elevated intra-ocular pressure in patients suffering from open angle glaucoma and from ocular hypertension.

4.2 Posology and method of administration.

Recommended dose for adults (including elderly people): the recommended dose is one drop in the affected eye(s) once a day. The best effect is obtained administering Latanostill in the evening.

The posology of Latanostill should not be superior to one daily administration, as it has been demonstrated that more frequent administrations reduce the hypotensive effect on the intraocular pressure.

If one dose is forgotten, the treatment must continue normally with the following dose.

As for other eye-drops, it is recommended to press the lachrymal sac, on the medial canthus (where eyelids close) for one minute to reduce the possibility of systemic absorption. This procedure should be done soon after drop administration.

Contact lenses should be removed before application and may be applied after 15 minutes (see also section 4.4).

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

Paediatric population: No data about tolerability and efficacy in paediatric patients are available.
Therefore the use of Latanostill in children is not recommended.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

4.3 Contraindications. Hypersensitivity to any of the ingredients of Latanostill.

4.4 Special warnings and precautions for use. Latanoprost may alter the colour of the eye gradually by increasing the amount of brown pigment of the iris. Before starting the treatment, patients should be informed about the possibility of permanent change of the eye colour. The unilateral treatment may cause a permanent heterochromia.
This change of the eye colour has been noted mainly in patients with inhomogeneous-coloured irises, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies carried out on latanoprost the darkening usually begins with the first 8 months of treatment, rarely during the second or third year, and it has not been observed after the fourth year of treatment. The progression of iris pigmentation increase decreases with time and becomes stable after five years. The effects of increased pigmentation over five years are not available. On an open clinical study on latanoprost lasted five years to validate its safety, 33% of patients developped iris pigmentation (see 4.8). In most cases the iris colour change is slight and often not clinically observable. The incidence varies between 7% to 85% in patients with inhomogeneous-coloured irises, with major incidence in patients with yellow-brown irises. No change has been reported in patients with

homogeneous-coloured blue eyes and rarely in patients with homogeneous-coloured grey, green or brown eyes.

The colour change is due to increased melanin content in stromal melanocytes of the iris and not to an increase in the number of melanocytes. Usually the brown pigment around the pupil spreads concentrically towards the peripheral part of the affected eye, but it may concern the whole or sectors of the iris.
After discontinuing the treatment no further pigmentation increase has been found. Clinical studies available up to now have demonstrated that the colour change is not related to any symptom or pathologic alteration.
Iris naevi or freckles have not been influenced by the treatment. Clinical studies have not reported pigment accumulation in sclera-corneal trabeculate or in any other part of the anterior chamber.
It has not beendemonstrated that the darkening of the iris may cause any bad clinical consequence and the use of latanoprost may be continued if the aforementioned darkening occurs.
Patients must be checked regularly and in case of worsening of the clinical picture the use of Latanostill may be discontinued.

Limited experience of use of eye-drops containing latanoprost in chronic closed-angle glaucoma, in pseudo-aphakic patients with open-angle glaucoma and in pigmentary glaucoma exits. No experience of the use of Latanostill in inflammatory and neo-vascular glaucoma, in ocular flogosis conditions and in congenital glaucoma has been developed. Latanoprost has limited or no effect on the pupil, but insufficient experience relevant to closed-angle glaucoma acute attacks exists. Thus the use of Latanostill with caution in these circumstances must be cautious as long as experience with its use supply more concrete data.

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.

During the therapy with eye-drops containing latanoprost, notifications of ocular oedema may occur (see 4.8) principally in aphakic patients, pseudo-aphakic patients with ruptured posterior lens capsule or with anterior chamber lenses and in patients with known risk factors for cystoid macular oedema (as well as diabetic retinopathy and retina central vein occlusion).

Latanoprost must be used with precaution in aphakic patients, pseudo-aphakic patients with ruptured posterior lens capsule or with anterior chamber lenses and in patients with known risk factors for cystoid macular oedema.

Latanostill may be used with caution in patients with known risk factors for iritis / uveitis.

Limited experience relative to administration of latanoprost to patients with asthma is available, but several cases of asthma exacerbation and/or dyspnoea during post-marketing of latanoprost. Therefore patients suffering from asthma must be treated cautiously till sufficient experience is achieved; see also par. 4.8.

A peiriorbital cutis discolouration has been observed mainly in Japanese patients. Up to now data showed that the periorbital cutis discolouration is not permanent and in some cases it is reversible while continuing to use eye-drops containing latanoprost.

Latanoprost may gradually alter the eyelashes of the treated eye and surrounding area; these alterations include increase of length, thickness, pigmentation, number of eyelashes or hair and irregular growth of eyelashes. These alterations are reversible when the treatment is discontinued.

Latanostill contains benzalkonium chloride normally used as a preservative for ophthalmic drug products. It has been reported that benzalkonium chloride causes punctate keratopathy and/or toxic ulcerative keratopathy, may cause ocular irritation and alter the colour of soft contact lenses. A careful monitoring of patients suffering from ocular dryness who use Latanostill frequently and for prolonged periods, or in case of compromised cornea should be performed. As contact lenses can absorb benzalkonium chloride, patients should remove them before using Latanostill and may reinsert them after 15 minutes (see paragraph 4.2 “Posology and method of administration”).

Keep Latanostill out of the reach and sight of children.

4.5 Interaction with other medicinal products and other forms of interaction.

No conclusive results are available to evaluate interactions with other medicinal products.
Notifications of abnormal increase of the intra-ocular pressure after ophthalmic administration of two prostaglandin analogues at the same time. Therefore the use of two or more prostaglandins, of prostaglandin analogues or prostaglandins derivatives is not recommended.

4.6 Pregnancy and lactation
Pregnancy: Safety of Latanostill 50 µg/ml eye-drops during pregnancy has not been assessed. A potential pharmacological risk during pregnancy exists, both for foetus and for the newborn baby. Therefore Latanoprost should not be used during pregnancy.

Breast feeding: Latanoprost and its metabolites may be excreted in human milk, therefore Latanostill should not be used during lactation or lactation must be discontinued.

4.7 Effects on ability to drive and use machines. As usual in other ophthalmic medicinal products, instillation of eye-drops may cause temporary dimming of the eyesight.

4.8 Undesirable effects. The majority of reported undesirable effects affect the ocular system. In an open study to assess the safety of latanoprost lasted five years, 33% of patients developed iris pigmentation (see par. 4.4). Other ocular adverse reactions are generally transient and dose-related.

The adverse reactions are classified on the basis of frequency as follows: very common (= 1/10), common (= 1/100, < 1/10), uncommon (= 1/1000, < 1/100), rare (= 1/10000, < 1/1000) and very rare (< 1/10000).

	Very Common: (≥ 1/10)	*Common: (≥ 1/100 to < 1/10)*	*Uncommon: (≥1/1000 to <1/100)*	*Rare: (≥ 1/10000 to < 1/1000)*	*Very rare: (<1/10000)*
Eye disorders:	• increased pigmentation of the iris • slight or moderate conjunctival hyperaemia • ocular irritation (burning, stinging, sensation of foreign body) • changes of the eyelashes (lengthening, thickening, darkening, increased number of eyelashes)	• temporary punctate epithelial erosion (mainly asymptomatic), • blepharitis • ocular pain	• eyelid oedema; • ocular dryness; • keratitis; • blurred vision; • conjunctivitis	• iritis/uveitis (mainly in predisposed patients) • macular oedema, • symptomatic oedema and corneal erosion periorbital oedema, • eyelid skin darkening • eyelid skin reactions • altered eyelash orientation with consequent irritation • eyelid hair thickening, darkening and lengthening (mainly reported in Japan) • distichiasis	
Cardiac disorders:					• worsening of angina in patients with pre-existing pathology
Respiratory disorders:				• asthma (or its worsening) • dyspnoea	
Skin and subcutaneous tissues disorders:			• Rash	• Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelid	
General disorders:					• Thoracic pain

Post-marketing spontaneous notifications:

Nervous system troubles:
Headache, confusion.

Cardiopathies:
Palpitation.

Muscular, skeletal and connectival affections:
Myalgia, arthralgia.

Infections and infestations:
Herpetic keratitis.

4.9 Overdose. Apart from ocular irritation and conjunctival hyperaemia, other ocular undesirable effects in case of overdose of drugs containing latanoprost are not known. In case of accidental ingestion of Latanostill the following information might be useful: one bottle contains 125 µg of latanoprost.
More than 90% of the product is primarily metabolized by first pass effect through the liver. Intra-venous infusion of 3 µg/kg in healthy volunteers did not cause any symptoms, but a dose of 5.5-10 µg/kg caused nausea, abdominal pain, vertigo, weariness, hot flushes, sweating. In monkeys an intra-venous perfusion of latanoprost up to 500 µg/kg did not cause significant effects on cardio-vascular system.

Intra-venous administration of latanoprost in monkeys have been associated with transient broncho-constriction. However, if latanoprost is applied topically in the eye with a dose 7-fold higher than that used in clinical trials, it does not induce any broncho-constriction in patients suffering from moderate bronchial asthma.
If overdose with Latanostill occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *15.4.4 Prostaglandins analogue*.
ATC code: S01E E01

Mechanism of action:
Latanoprost active substance is an analogue of prostaglandin F2α, acting as a selective agonist to the prostanoid receptor FP
Pharmaco-dynamic effects:
Latanoprost reduces the intra-ocular pressure by increasing the outflow of aqueous humour. Decrease of intra-ocular pressure starts about 3-4 hours after administration in humans and reaches its maximum effect after 8/12 hours. The reached values lasts for 24 hours.

Studies on animals and humans show that the main mechanism of action is an increase in uveo-scleral outflow, even though in human an easier outflow (reduced resistance to outflow) has been reported.
Clinical efficacy and safety
Pilot studies have proved the efficacy of drugs containing latanoprost as monotherapy. Besides, clinical studies regarding combined use have been carried out. These include studies demonstrating efficacy of latanoprost associated with beta-adrenergic antagonists (timolol). Short term studies (1-2 weeks) show an additive effect of latanoprost if used in association with adrenergic agonists (dipivalyl epinephrine), carbonic anhidrase inhibitors administered orally (acetazolamide) and, at least partially, with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the aqueous humour production. No effect of latanoprost on hemato-aqueous barrier has been reported.

Studies on monkeys have proved that latanoprost, administered in clinical doses has no or negligible effects on intra-ocular blood circulation. Slight or moderate conjunctival or episcleral hyperemia is possible during topic treatment.

Chronic treatment with latanoprost in monkey eye after extracapsular crystalline lens extraction did not affect the retinal blood circulation as verified by fluorangiography.

During short term treatments latanoprost did not induce diffusion of fluorescein in the posterior segment in human pseudophakic eyes.

Significant pharmacological effects on cardiovascular or respiratory systems after administration of latanoprost at clinical doses have not been reported.

5.2 Pharmacokinetic properties. Latanoprost (m.w. 432.58) is a pro-drug esterified with an isopropyl group, inactive in itself, which after hydrolysis to its acid form becomes biologically active.

Absorption
The pro-drug is well absorbed through the cornea and is entirely hydrolyzed during its passage in the aqueous humor.
Distribution
Studies on human shown that the concentration peak in the aqueous humour is reached about two hours after the topical administration. After local instillation in the monkey, latanoprost distributes mainly in the anterior segment, in the conjunctiva and in the eyelids. Only small amounts of drug reach the posterior segment.
Biotransformation
The active form of latanoprost is not practically metabolised in the eye, but mainly in the liver.
Elimination
In humans plasmatic half-life is 17 minutes. Studies on animals have shown that the main metabolites, 1.2-dinor and 1,2,3,4-tetranor, have no or slight biological activity and are mainly excreted in urine.

5.3 Preclinical safety data. Ocular toxicity of latanoprost as well as systemic toxicity, has been evaluatied on many animal species. In general latanoprost is well tolerated with a safety range between ocular clinical dose and systemic toxicity of at least 1000 times. High doses of latanoprost, about 100-fold its clinical dose/kg of body weight, administered intravenously in non-anaesthetized monkeys, caused an increase in respiratory frequency probably due to brief bronchoconstriction. In animals studies latanoprost did not show sensitizing properties.

No toxic effects in the eye with doses up to 100 µg/eye/day in rabbits or monkeys (clinical dose is approximately 1.5µg/eye/day) have not been reported. However in monkeys latanoprost proved to cause an increase in iris pigmentation.

The hyperpigmentation seems to be caused by an increased production of melanin in stromal melanocytes of the iris; proliferative alterations have not been reported. The colour change of the iris may be permanent.
Research on chronic ocular toxicity have shown that the administration of 6 µg/eye/day of latanoprost may cause an enlargement of rima palpebrarum. This effect has nor been reported in humans.

Latanoprost resulted negative in bacterial reverse mutation test, in murine lymphoma gene mutation test and in mouse micro-nucleus tests. Chromosomal aberrations on human lymphocytes have been observed *in vitro*. Similar effects have been observed with prostaglandin F2α, a natural origin prostaglandin; this indicates that these effects are class-related.

Further mutagenesis studies *in vitro/in vivo* on rats, on programmed DNA synthesis gave negative results and indicated that latanoprost has no mutagenic properties. Carcinogenesis studies on mice and rats resulted negative.

Studies on animals have demonstrated that latanoprost has no effect on male or female fertility. In embryonal toxicity studies on rats no embryonal toxicity has been assessed with doses of latanoprost of 5, 50 and 250 µg/kg/day by intravenous injection.

However latanoprost causes lethal effects on rabbit embryon at 5 µg/kg/day and higher. A 5 µg/kg/day dose (about 100-fold the clinical dose) caused significant embryonal and foetal toxicity characterized by increased incidence of delayed reabsorption, abortion and reduced foetal weight.

No teratogenic potential has resulted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients. sodium chloride, benzalkonium chloride, sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium hydroxide and/or phosphoric acid, purified water.
6.2 Incompatibilities. In vitro studies have shown that a precipitate forms if eye-drops containing thymerosal are mixed with eye-drops containing latanoprost. If these medicinal products are used, eye-drops are to be administered at least 5 minutes apart.
6.3 Shelf life
As packaged for sale: 36 months
After first opening: 4 weeks
6.4 Special precautions for storage. Store the unopened bottles in the refrigerator at +2°C - +8°C). Once a bottle is opened for use, it must be stored at temperature lower than 25°C and can be used within 4 weeks.
6.5 Nature and contents of container. Polyethylene bottles fitted with a dropper and polypropylene cap with polyethylene seal.
Each bottle with dropper contains 2.5 ml of eye-drops solution corresponding to about 80 drops.
Pack: 1 bottle of 2.5 ml.
6.6 Special precautions for disposal and other handling. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PORTUGUESE MARKETING AUTHORISATION HOLDER. BRUSCHETTINI S.r.l. - Via Isonzo 6 -16147 Genova (Italy)

8. ITALIAN MARKETING AUTHORISATION NUMBER. 042281016 – 50 micrograms/ml eye-drops, solution – 1 PE bottle of 2,5 ml

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
April 2013

10. DATE OF REVISION OF THE TEXT
July 2013