1. NAME OF THE MEDICINAL PRODUCT

OPTINAS PLUS (LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Latanoprost USP..... %W/V
Timolol Maleate USP
Eq. To Timolol.. .....% W/V
Benzalkonium Chloride Solution NF.....% W/V
(As Preservative)
Sterile Aqueous Base .....Q.S.

3. PHARMACEUTICAL FORM

Ophthalmic (Eye Drop)

4. Clinical particulars

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP), in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

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.

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Pediatric population

The safety and efficacy in children and adolescents has not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product.

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

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

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION is contraindicated in patients with:

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with a pace-maker, overt cardiac failure, cardiogenic shock.
- Hypersensitivity to the active substances (latanoprost or timolol) or to any of the excipients

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, latanoprost and timolol are absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina, and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Cardiac reactions, and rarely, death in association with cardiac failures have been reported following administration of timolol.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta- blockers.

LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.

Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and

unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy

Timolol may interact with other drugs.

The use of two local beta-blockers or two local prostaglandins is not recommended.

Ocular effects

Latanoprost may gradually change the eye colour by increasing the amount of brown pigment in the iris. Similar to experience with latanoprost eye drops, increased iris pigmentation was seen in 16-20% of all patients treated with LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution for up to one year (based on photographs). This effect has predominantly been seen in patients with mixed coloured irides, i.e. green-brown, yellow-brown or blue/grey-brown, and is due to increased melanin content in the stromal melanocytes of the iris. 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 homogeneously blue, grey, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials with latanoprost.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.

No further increase in brown pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

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 but 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 colour. Unilateral treatment can result in permanent heterochromia.

There is no documented experience with latanoprost in inflammatory, neovascular, or chronic angle closure glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost has no or little effect on the pupil but there is no documented experience in acute attacks of closed angle glaucoma. It is recommended, therefore, that LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution should be used with caution in these conditions until more experience is obtained.

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.

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. Latanoprost / Timolol should be used with caution in these patients.

Use of contact lenses

LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution but may be reinserted after 15 minutes

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Latanoprost / Timolol.
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.
The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION
is given to patients already receiving an oral beta-adrenergic blocking agent, and the use of two or more topical beta-adrenergic blocking agents is not recommended.
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta- blockers solutions are administered concomitantly with oral calcium channel blockers, guanethidine or beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides or parasympathomimetics.
Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.
The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.
Beta-blockers may increase the hypoglycaemic effect of anti-diabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

4.6 Pregnancy and Lactation

Pregnancy

Latanoprost

There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Timolol

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption.

Epidemiological studies have not revealed malformative effects, but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution is administered until delivery, the neonate should be carefully monitored during the first days of life.

Consequently LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution should not be used during pregnancy.

Breastfeeding

Beta- blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption.

Latanoprost and its metabolites may pass into breast milk. LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution should not be used in women who are breast-feeding.

Fertility

There are no human data on the effects of LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution on fertility.

4.7 Effects on ability to drive and use machines

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

For latanoprost, the majority of adverse events relate to the ocular system. In data from the extension phase of Latanoprost / Timolol pivotal trials, 16 - 20% of patients developed increased iris pigmentation, which may be permanent. In an open 5 year latanoprost safety study, 33% of patients developed iris pigmentation. Other ocular adverse events are generally transient and occur on dose administration. For timolol, the most serious adverse events are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospam and allergic reactions.

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.
Treatment related adverse events seen in clinical trials with LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution are listed below.

Adverse events are categorized by frequency as follows: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10,000, <1/1000) and very rare (<1/10,000). Not known (cannot be estimated from the available data).

Infections and Infestations	*Not known:*	Herpetic keratitis
Nervous System Disorders	*Not known:*	Headache, Dizziness
Eye Disorders	*Very common:*	Increased iris pigmentation; mild to moderate conjunctival hyperaemia, eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).
	Common:	Transient punctate epithelial keratitis, mostly without symptoms; blepharitis; eye pain, photophobia.
	Uncommon:	Eyelid oedema, dry eye; keratitis; vision blurred; conjunctivitis.
	Rare:	Iritis/uveitis (the majority of reports in patients with concomitant predisposing factors); macular oedema; symptomatic corneal oedema and erosions; periorbital oedema; misdirected eyelashes sometimes resulting in eye irritation; extra row of cilia at the aperture of the meibomian glands (distichiasis).

	Very rare:	Periorbital and lid changes resulting in deepening of the eyelid sulcus.
	Not known:	Iris cyst
Cardiac Disorders:	*Very rare:*	Unstable angina.
	Not known:	Palpitations.
Respiratory, Thoracic and Mediastinal Disorders:	*Rare:*	Asthma, asthma exacerbation and dyspnoea.
Skin and Subcutaneous Tissue Disorders:	*Uncommon:*	Skin rash.
	Rare:	Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids.
Musculoskeletal and Connective Tissue Disorders:	*Not known:*	Myalgia; Arthralgia.
General Disorders and Administration Site Conditions:	*Very rare:*	Chest pain.
Gastrointestinal disorders	*Uncommon:*	Nausea; vomiting.

c. Description of selected adverse reactions

No information is provided.

d. 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 5.1). Adverse events seen more frequently in the paediatric population as compared to adults are: nasopharyngitis and pyrexia. 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.

4.9 Overdose

No data are available in humans with regard to overdose with LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution.

Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur the treatment should be symptomatic and supportive. Studies have shown that timolol does not dialyse readily.

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are

known if latanoprost is overdosed.
If latanoprost is accidentally ingested orally the following information may be useful:
Treatment: Gastric lavage if needed. Symptomatic treatment. Latanoprost is extensively 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. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group:

Ophthalmological-betablocking agents - timolol, combinations.

ATC code: S01ED51

Mechanism of action

LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

Latanoprost, a prostaglandin F2alpha analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. 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.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers IOP by decreasing the formation of aqueous in the ciliary epithelium.

The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been found to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical effects

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.

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.

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 at random either latanoprost 50 mcg/ml 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 intraocular pressure (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 (see table) and was maintained throughout the 12 week period of study, as in adults.

Table: 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 an analysis of covariance (ANCOVA) model.

5.2 Pharmacokinetic properties

Latanoprost

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

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.

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 50 mcg/ml, 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 4.9). 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.

Timolol

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose

LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION:

No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-

4 hours after administration LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution compared to monotherapy.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered Timolol topically in studies lasting one and two years, respectively. The oral LD50 of the drug is 1,190 and 900 mg/kg in female mice and female rats, respectively.

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 embryofetal toxicity characterised by increased incidence of late resorption and abortion and by reduced fetal weight.
No teratogenic potential has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Dihydrogen Phosphate
Anhydrous Disodium Hydrogen Phosphate
Hydroxy Propyl Betacyclodextrin
Sodium Hydroxide Pellets
Hydrochloric Acid
Purified Water

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Latanoprost and Timolol Maleate Eye Drops Solution. If such drugs are used concomitantly with LATANOPROST & TIMOLOL MALEATE OPHTHALMIC SOLUTION, Solution, they should be administered with an interval of at least five minutes.

6.3 Shelf life

24 months for the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

2.5ml filled in 5ml sterile Novelia opaque plastic bottle with nozzle & cap

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7

Applicant
PHARMACY PLUS LIMITED, 18,
MOJIDI STREET, OFF TOYIN STREET,
IKEJA-LAGOS. 19501142
info@pharplusltd.com

Manufacturer
INDIANA OPTHALMICS,
Plot No.136-137,Wadwan City-363 035,Surendranagar.Gujarat.Indian,
India 2752241554 indianaophthalmics@yahoo.co.in