Combi-Prost

Latanoprost & Timolol

NAME OF THE MEDICAL PRODUCT

Combi-Prost Eye Drops

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50mcg of Latanoprost and 6.8 mg of timolol maleate, equivalent to 5.0 mg timolol.

PHARMACEUTICAL FORM

Eye drop solution.

The solution is a clear, colourless liquid.

CLINICAL PARTICULARS

Therapeutic Indications

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

Posology and Method of Administration

Recommended dosage for adults (including the elderly):

The recommended dose is one eye drop in the affected eye(s), once daily.

If a dose is missed, treatment should continue with the next dose as normal. The dose should not exceed one drop in each affected eye daily.

Administration:

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.

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.

<u>Use in children and adolescents:</u>

The safety and efficacy in children and adolescents have not been established.

Contraindications

Combi-Prost 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 pace-maker, overt cardiac failure, cardiogenic shock.
- Hypersensitivity to the active substances or to any of the excipients.

Special Warnings and Precautions for Use

Systemic effects

Like other topically applied ophthalmic agents, Combi-Prost is 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. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see *section Posology and Method of Administration*.

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 monitored closely 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. Combi-Prost 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.

Hypoglycemia/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.

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 exaggerated when Combi-Prost 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 (see *section Interactions*).

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 see *section Interactions*.

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

Ocular effects

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. 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 iris 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 the 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. Therefore it is recommended that Combi-Prost 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. Combi-Prost should be used with caution in these patients.

Use of contact lenses

Combi-Prost contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctuate 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 Combi-Prost in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before instillation of Combi-Prost but may be reinserted after 15 minutes (see *section Posology and Method of Administration*).

Interactions

No specific drug interaction studies have been performed with Combi-Prost.

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.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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 effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when Combi-Prost is administered in patients already receiving an oral beta-adrenergic blocking agent and topical use of two or more beta-adrenergic blocking agents is not recommended.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

The hypertensive reaction to sudden discontinuation of clonidine administration can be potentiated when taking beta-blockers.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta blockers can mask the signs and symptoms of hypoglycaemia (see *section Special Warnings and Precautions for Use*).

Pregnancy and Lactation

Pregnancy

Latanoprost:

There are no adequate data for 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, see *section Posology and Method of Administration.*

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 neonates when beta-blockers have been administered until delivery. If Combi-Prost is administered until delivery, the neonate should be carefully monitored during the first days of life.

Consequently, Combi-Prost should not be administered during pregnancy.

Lactation

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, see section *Posology and Method of Administration*.

Latanoprost and its metabolites may pass into breast milk. Combi-Prost should therefore not be used in women who are breast-feeding.

Fertility

Neither Latanoprost nor timolol have been found to have any effect on male or female fertility in animal studies.

Effects on Ability to Drive and Use Machines

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.

Undesirable Effects

For latanoprost, the majority of adverse reactions relate to the ocular system. Some patients with latanoprost/timolol eye drops developed increased iris pigmentation, which may be permanent.Some patients with latanoprost also developed iris pigmentation (see *Section Special Warnings and Precautions for Use*). Other ocular adverse reactions are generally transient and occur on dose administration. For timolol, the most serious adverse reactions are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospasm and allergic reactions.

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar adverse reactions as seen with systemic beta blocking agents. 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 reactions observed with latanoprost and timolol are listed below.

Nervous system disorders:

Headache

Eye Disorders:

Increased iris pigmentation, eye irritation (stinging, burning sensation and pruritus), eye pain, ocular hyperaemia, conjunctivitis, blurred vision, lacrimation increased, blepharitis, corneal disorders.

Skin and subcutaneous tissue disorders:

Skin rash, pruritus.

Additional adverse reactions have been reported specific to the use of the individual components of latanoprost/timolol eye drops are listed below.

For latanoprost, these are:

Infections and infestations:

Herpetic keratitis

Nervous system disorders:

Dizziness

Eye disorders:

Eyelash and vellus hair changes (increased in length, thickness, pigmentation, and number), punctate corneal epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus.

Cardiac disorders:

Aggravation of angina in patients with pre-existing disease, palpitations

Respiratory, thoracic and mediastinal disorders:

Asthma, asthma aggravation, dyspnoea

Skin and subcutaneous tissue disorders:

Darkening of palpebral skin.

Musculoskeletal and connective tissue disorders:

Join pain, muscle pain.

General disorders and administration site conditions:

Chest pain

For timolol, these are:

Immune system disorders:

Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Hypoglycaemia

Psychiatric disorders:

Insomnia, depression, nightmares, memory loss.

Nervous system disorders:

Syncope, cerebrovascular accident cerebral ischemia, increases in signs and symptoms of myasthenia gravis, dizziness, paraesthesia and headache.

Eye disorders:

Signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see *section Special Warnings and Precautions for Use*), decreased corneal sensitivity, dry eye, corneal erosion, ptosis, diplopia.

Ear and labyrinth disorders:

Tinnitus

Cardiac disorders:

Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.

Vascular disorders:

Hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Gastrointestinal disorders:

Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders:

Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.

Musculoskeletal and connective tissue disorders:

Myalgia

Reproductive system and breast disorders:

Sexual dysfunction, decreased libido

General disorders and administration site conditions:

Asthenia/fatigue

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.

Overdose

No data are available in humans with regard to overdose with Combi-Prost.

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 adverse reactions have been observed after overdose with latanoprost.

If latanoprost is accidentally ingested 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 microgram/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 microgram/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. These symptoms were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Properties

Pharmacotherapeutic group: Ophthalmological-beta-blockers-timolol combinations.

ATC Code: S01 ED51

Mechanism of Action

Combi-Prost contains two active substances: latanoprost and timolol maleate. These two components decrease the elevated intraocular pressure by different mechanisms of action, and the combined effect results in additional intraocular pressure reduction compared to either compound administered alone.

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. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in 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 blocker that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers intraocular pressure 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 rate 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 ocular blood flow after chronic treatment.

Pharmacokinetics Properties

Latanoprost:

Latanoprost is an isopropyl ester prodrug, which *per se* is inactive, but after hydrolysis to latanoprost acid, becomes biologically active. The prodrug is well absorbed through the cornea and all the quantity of the drug that enters the aqueous humour is hydrolysed during its passage through the cornea. Clinical studies in man indicate that the peak concentration in the aqueous humour, approximately 15-30 ng/ml, is reached about two hours after topical administration of latanoprost alone. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids.

Latanoprost acid has a plasma clearance of 0.40 l/h/kg and a small volume of distribution (0.16 l/kg), resulting in a rapid half life in plasma of 17 minutes. After topical ocular administration the systemic bioavailability of latanoprost acid is 45%. Binding of latanoprost acid to plasma proteins is 87%.

There is practically no metabolism of the latanoprost acid in the eye. The main metabolism occurs in the liver. 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 predominantly in the urine.

Timolol

The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically, and a maximum plasma concentration of 1 ng/ml is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half life of timolol in plasma is

approximately 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some amount of unchanged timolol.

Latanoprost and timolol combination

No pharmacokinetic interactions between latanoprost and timolol were observed although there was an approximate 2-fold increase in the latanoprost acid concentration in aqueous humour 1-4 hours after administration of latanoprost and timolol combination compared to monotherapy.

PHARMACEUTICAL PARTICULARS

List of Excipients

Benzalkonium Chloride

Sodium Chloride

Disodium phosphate anhydrous

Sodium dihydrogen phosphate monohydrate

Sodium hydroxide solution (for adjustment to pH 6.0)

Hydrochloric acid solution (for adjustment to pH 6.0)

Water for injection

Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Latanoprost. If such drugs are used concomitantly with Combi-Prost, the eye drops should be administered with an interval of at least five minutes.

Shelf life

Please refer to outer carton for shelf life.

Storage Conditions

Store unopened bottle at 2°C to 8°C.

Store opened bottle below 25°C. Use within 4 weeks after opening.

Protect from light.

Nature and Contents of Container

Each bottle contains 2.5 mL eye drops corresponding to a minimum of 80 drops of solution. One drop contains approximately 1.5 mcg Latanoprost and 150mcg Timolol.

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