

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved

1. NAME OF THE MEDICINAL PRODUCT

XALACOM® eye drops.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml solution contains latanoprost 50 micrograms and timolol maleate 6,8 mg equivalent to 5 mg timolol.

Excipient: Benzalkonium chloride 200 microgram/ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

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.

4.2. Posology and method of administration

Posology 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 effected eye(s) daily, since it has been shown that more frequent administration of latanoprost decreases the intraocular pressure lowering effect.

Method of administration:

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes. (see section 4.4)

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.

Paediatric population:

The safety and efficacy of XALACOM® eye drops in children below 18 years of age has not been established.

4.3. Contraindications

XALACOM® is contraindicated in patients with:

- Reactive airway disease including bronchial asthma or 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.

4.4. Special warnings and special precautions for use

Systemic effects:

Like other topically applied ophthalmic agents, XALACOM® 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 4.2.

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. XALACOM® 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-adrenergic blocking agents may increase the hypoglycemic effect of agents used to treat diabetes, and can mask the signs and symptoms of hypoglycemia. They should be used with caution in patients with spontaneous hypoglycemia or diabetes (especially those with labile diabetes), who are receiving insulin or oral hypoglycemic agents.

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

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 (see section 4.5).

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.

A gradual withdrawal of beta-adrenergic blocking agents prior to major surgery should be considered. Beta-adrenergic blocking agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, which may augment the risk of general anesthesia in surgical procedures. Prolonged severe hypotension during anesthesia and difficulty restarting and maintaining the heartbeat have been reported. During surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Concomitant therapy:

Timolol may interact with other drugs see 4.5 Interaction with other medicinal products and other forms of interaction.

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. Similar to experience with latanoprost eye drops, increased iris pigmentation was seen in 16-20% of all patients treated with XALACOM® 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 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 XALACOM® should be used with caution in these conditions until more experience is obtained.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

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. XALACOM® should be used with caution in these patients.

Use of contact lenses:

XALACOM® 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 XALACOM® 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 XALACOM® but may be reinserted after 15 minutes (see section 4.2 Posology and Method of Administration).

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

No specific drug interaction studies have been performed with XALACOM®.

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, antiarrhythmics (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 Xalacom 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.

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 (see 4.4 Special warnings and special precautions for use).

4.6. Fertility, pregnancy and lactation

Fertility:

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Pregnancy

Latanoprost:

There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). 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 4.2.

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 XALACOM® is administered until delivery, the neonate should be carefully monitored during the first days of life.

Consequently Xalacom should not be used during pregnancy (see 5.3).

Lactation

Latanoprost and its metabolites may pass into breast milk.

Timolol maleate has been detected in human milk following oral and ocular drug administration. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 the XALACOM® 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 (see 4.4). 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, bronchospasm 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. 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 XALACOM® are listed below.

Adverse events are categorized by frequency as follows: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$).

Nervous System Disorders

Uncommon: Headache.

Eye Disorders

Very common: Increased iris pigmentation.

Common: Eye irritation (including stinging, burning and itching), Eye pain

Uncommon: Eye hyperaemia, Conjunctivitis, Vision blurred, Lacrimation increased, Blepharitis, Corneal disorders

Skin and Subcutaneous Tissue Disorders

Uncommon: Skin rash, Pruritus

Additional adverse events have been reported specific to the use of the individual components of Xalacom in either in clinical studies, spontaneous reports or in the available literature.

For latanoprost, these are:

Infections and Infestations:

Herpetic Keratitis

Nervous System Disorders:

Dizziness.

Eye Disorders:

Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), Punctate epithelial erosions, periorbital and eyelid oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema) , including cystoid macular edema, 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, acute asthma attacks , dyspnoea.

Skin and Subcutaneous Tissue Disorders:

Darkening of the palpebral skin of the eyelids and localized skin reaction on the eyelids.

Musculoskeletal and Connective Tissue Disorders:

Joint pain, muscle pain.

General disorders and Administration Site Conditions:

Non-specific chest pain

For timolol, these are:

Immune System Disorders:

Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Anorexia, hypoglycaemia, masked symptoms of hypoglycemia in diabetic patients (see 4.4 Special warnings and special precautions for use)

Psychiatric Disorders:

Behavioral changes and psychic disturbances including, confusion, hallucinations, anxiety, disorientation, nervousness, decreased libido, insomnia, depression, nightmares, memory loss.

Nervous System Disorders:

Syncope, cerebrovascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, dizziness, paresthesia, somnolence and headache.

Eye Disorders:

Cystoid macular edema, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity, dry eyes, corneal erosion, ptosis, visual disturbances including refractive changes and diplopia.

Ear and Labyrinth Disorders:

Tinnitus.

Cardiac Disorders:

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

Vascular Disorders:

Claudication, hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, Thoracic and Mediastinal Disorders:

Bronchospasm (predominately in patients with pre-existing bronchospastic disease), dyspnoea, cough, nasal congestion, pulmonary edema, and respiratory failure.

Gastrointestinal Disorders:

Dysgeusia, nausea, dyspepsia, diarrhoea, , dry mouth, abdominal pain, vomiting and retroperitoneal fibrosis.

Skin and Subcutaneous Tissue Disorders:

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

Musculoskeletal and connective tissue disorders:

Systemic lupus erythematosus and myalgia.

Reproductive system and breast disorders:

Sexual dysfunction, impotence, decreased libido and Peyronie's disease.

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.

4.9. Overdose

No data are available in humans with regard to overdose with XALACOM®.

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 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological – beta-blocking agents – timolol, combinations

ATC code: S01ED51

Mechanism of action

XALACOM® 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 F_{2α} 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.

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

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.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous (See section 4.3 Contraindications and section 4.4 Special Warnings and Special Precautions for Use – Timolol Maleate).

Timolol maleate ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

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

In dose finding studies, XALACOM® produced significantly greater decreases in mean diurnal IOP compared to latanoprost and timolol administered once daily as monotherapy. In two well controlled, double masked six-month clinical studies the IOP reducing effect of XALACOM® was compared with latanoprost and timolol monotherapy in patients with an IOP of at least 25 mm Hg or greater. Following a 2-4 week run-in with timolol (mean decrease in IOP from enrollment of 5 mm Hg), additional decreases in mean diurnal IOP of 3.1, 2.0 and 0.6 mm Hg were observed after 6 months of treatment for XALACOM®, latanoprost and timolol (twice daily), respectively. The IOP lowering effect of XALACOM® was maintained in 6 month open label extension of these studies.

Existing data suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, when considering a recommendation of either morning or evening dosing, sufficient consideration should be given to the lifestyle of the patient and their likely compliance.

It should be kept in mind that in case of insufficient efficacy of the fixed combination, results from studies indicate that the use of unfixed administration of Timolol bid and latanoprost once a day might be still efficient.

Onset of action of XALACOM® is within one hour and maximal effect occurs within six to eight hours. Adequate IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2. Pharmacokinetic properties

Latanoprost

Latanoprost is an isopropyl ester prodrug, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through the cornea. Studies in man indicate that the maximum concentration in the aqueous humour, approximately 15-30 ng/ml, is reached about 2 hours after topical administration of latanoprost alone. After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost 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, 17 minutes. After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.

There is practically no metabolism of the acid of latanoprost 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 primarily 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 about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

XALACOM®

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 of XALACOM® compared to monotherapy.

5.3. Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. No adverse ocular or systemic effects were seen in rabbits treated topically with the fixed combination or with concomitantly administered latanoprost and timolol ophthalmic solutions. Safety pharmacology, genotoxicity and carcinogenicity studies with each of the components revealed no special hazards for humans. Latanoprost did not affect corneal wound healing in the rabbit eye, whereas timolol inhibited the process in the rabbit and the monkey eye when administered more frequently than once a day.

For latanoprost, no effects on male and female fertility in rats and no teratogenic potential in rats and rabbits have been established. No embryotoxicity was observed in rats after intravenous doses of up to 250 micrograms/kg/day. However, latanoprost caused embryofetal toxicity, characterised by increased incidence of late resorption and abortion and by reduced foetal weight, in rabbits at intravenous doses of 5 micrograms/kg/day (approximately 100 times the clinical dose) and above.

Timolol showed no effects on male and female fertility in rats or teratogenic potential in mice, rats and rabbits.

Latanoprost-

Systemic/Ocular Effects:

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 unanesthetized monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In monkeys, latanoprost has been infused intravenously in doses of up to 500 mcg/kg without major effects on the cardiovascular system. In animal studies, latanoprost has not been found to have sensitizing 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). Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.

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.

Carcinogenesis:

Carcinogenicity studies in mice and rats were negative.

Mutagenesis:

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 F₂ α , 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.

Teratogenesis:

No teratogenic potential has been detected.

Timolol Maleate-

Carcinogenesis:

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol maleate at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans.

Mutagenesis:

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol maleate employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Teratogenesis:

Teratogenicity studies with timolol maleate in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzalkonium chloride, Disodium phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium chloride, , Water for injections.

6.2. Incompatibilities

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

6.3. Shelf life

2 years

After opening of container: 4 weeks

6.4. Special precautions for storage

Store unopened bottle(s) under refrigeration at 2°C to 8°C.

After first opening the container, store below 25°C and use within four weeks.

Keep the bottle in the outer carton in order to protect from light.

6.5. Nature and content of container

LDPE bottle (5ml) and dropper applicator (dropper tip), HDPE screw cap, tamper evident LDPE overcap. Each bottle contains 2,5 ml eye drop solution.

6.6. Instructions for use and handling

The tamper evident overcap should be removed before use.

MANUFACTURER

Pfizer Manufacturing, NV/SA, PUURS, Belgium

LICENSE HOLDER: Pfizer Pharmaceuticals Israel Ltd.

9 Shenkar St., Herzliya Pituach, 46725