

DATA SHEET

XALAPLUS[®] Eye Drops

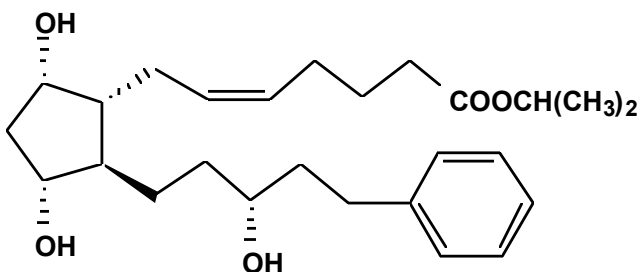
(latanoprost 50µg/mL and timolol 5mg/mL)

For further information about the component products contained in XALAPLUS refer to latanoprost and timolol individual Data Sheet documents.

NAME OF THE DRUG

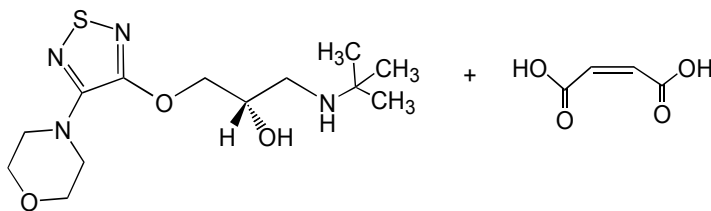
XALAPLUS is a combination eye drop containing latanoprost and timolol maleate.

Latanoprost



The chemical name of latanoprost is isopropyl-(Z)-7[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenyl-1-pentyl]cyclopentyl]-5-heptenoate, according to IUPAC. Its molecular formula is C₂₆H₄₀O₅. The CAS number for latanoprost is 130209-82-4.

Timolol maleate



The chemical name of timolol maleate is (S)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Its molecular formula is C₁₃ H₂₄ N₄ O₃ S•C₄ H₄ O₄. The CAS number for timolol maleate is 26921-17-5.

DESCRIPTION

The active ingredients in XALAPLUS eye drops are latanoprost and timolol maleate. Latanoprost is a prostaglandin F_{2α} analogue. It has a molecular weight of 432.58. It is a colourless to slightly yellow oil which is practically insoluble in water, freely soluble in ethanol, ethyl acetate, isopropanol, methanol, acetone and octanol, and very soluble in acetonitrile.

Sixty four isomers of latanoprost are possible however, for XALAPLUS it is purified as a single isomer.

Timolol maleate is a beta-adrenergic receptor blocking agent. It has a molecular weight of 432.50. It is a white to off-white crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

XALAPLUS is a sterile, isotonic solution containing 50 micrograms/mL of latanoprost and 5mg/mL of timolol (6.83mg timolol maleate) in an aqueous buffer solution of pH 6.0. The excipients in XALAPLUS are sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injections and benzalkonium chloride (0.20mg/mL) as a preservative agent.

The solution is a clear and colourless liquid, filled in a polyethylene container.

PHARMACOLOGY

Pharmacodynamics

XALAPLUS 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

Latanoprost is a selective prostanoid F_{2α} receptor agonist which reduces IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. In addition, 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 or the blood-aqueous barrier. Latanoprost has no or negligible effects on the intraocular blood circulation when used at the human clinical dose, as 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 pharmacologic effects on the cardiovascular or respiratory systems.

Timolol

Timolol maleate is a beta₁ and beta₂ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by decreasing the formation of aqueous humour in the ciliary epithelium. The precise mechanism of action is not clearly established.

XALAPLUS

Onset of action of XALAPLUS 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.

PHARMACOKINETICS

Latanoprost

Latanoprost is an isopropyl ester pro drug which is inactive, but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active.

The pro drug 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, approximately 30ng/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 eye lids. Only minute quantities of the drug reach the posterior segment.

Reduction of the intraocular pressure in man starts about three to four hours after administration of latanoprost alone and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

The acid of latanoprost has a plasma clearance of 0.40L/h*kg and a small volume of distribution, 0.16L/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 1ng/mL is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300µg/day). The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in urine together with some unchanged timolol.

XALAPLUS

No pharmacokinetic interactions between latanoprost and timolol have been observed although the aqueous humour concentrations of the acid of latanoprost tended to be higher 1 to 4 hours after administration of the combination product compared to monotherapy with either agent.

CLINICAL TRIALS

Two 6-month, randomised, double-blind, multicentre clinical studies were conducted to compare the IOP-lowering effect of XALAPLUS dosed once daily to latanoprost 0.005% dosed once daily and timolol 0.5% dosed twice daily.

The inclusion criteria for patients in both studies consisted of adults with diagnoses of primary open angle glaucoma, pigmentary glaucoma, capsular glaucoma or ocular hypertension. Patients previously on IOP reducing therapy required an IOP at enrolment of ≥ 25 mmHg. Patients not previously on IOP reducing therapy required an IOP of ≥ 30 mmHg on enrolment. In the two studies, 92% and 84% of patients were reported to have been on IOP reducing therapy within 3 months prior to study start. Approximately 70% of these patients were on timolol therapy.

The mean diurnal IOP-lowering effect of XALAPLUS was greater (1 to 3mmHg) than that produced by monotherapy with either latanoprost 0.005% or timolol 0.5%. However, there are no data to show the optimal dose of these agents in combination.

Open label extensions of the 2 studies mentioned above were conducted for up to an additional 6 months. The IOP lowering effect of XALAPLUS was maintained during this period.

INDICATIONS

Reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications. XALAPLUS should not be used to initiate therapy.

CONTRAINDICATIONS

- reactive airway disease including bronchial asthma, a history of bronchial asthma, or 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, or cardiogenic shock.
- known hypersensitivity to any component in XALAPLUS.

PRECAUTIONS

Systemic effects

Cardiovascular/Respiratory reactions:

Like other topically applied ophthalmic agents, XALAPLUS may be absorbed systemically. Due to the beta-adrenergic component timolol, the same types of adverse reactions seen with systemic beta-blockers may occur including aggravation of Prinzmetal's angina, aggravation of severe peripheral and central circulatory disorders, bradycardia and hypotension.

Respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma and, death associated with cardiac failure have been reported following administration of timolol. Cardiac failure should be adequately controlled before treatment. Patients with a history of severe cardiac disease should be monitored closely for signs of cardiac failure.

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

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

Timolol maleate 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.^

A gradual withdrawal of beta-adrenergic blocking agents prior to major surgery may 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 anaesthesia in surgical procedures. Protracted severe hypotension during anaesthesia 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.

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.^

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, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy:

Timolol may interact with other drugs, see also Interactions with other drugs.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be exaggerated when XALAPLUS is given to patients already receiving an oral beta-blocking agent. There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more local beta-blockers or two or more local prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended.

Additional effects of beta-blockade:

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-blockers may increase the

hypoglycaemic effect of agents used to treat diabetes and may mask the signs and symptoms of acute hypoglycaemia.

Therapy with beta-blockers may mask certain signs and symptoms of hyperthyroidism and abrupt withdrawal of therapy may precipitate a worsening of symptoms.

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Ocular effects

Latanoprost may gradually change the 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 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.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost.

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.

There is no or limited experience with latanoprost or latanoprost-timolol in inflammatory, neovascular, chronic angle closure or congenital 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 experience in acute attacks of closed angle glaucoma. Therefore

it is recommended that XALAPLUS 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. XALAPLUS should be used with caution in these patients.

Choroidal detachment after filtration procedures has been reported with the administration of ocular hypotensive agents.

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

Use of contact lenses

XALAPLUS contains benzalkonium chloride which may be absorbed by contact lenses. Several contact lens soaking solutions contain thiomersal which may also form a precipitate with the benzalkonium chloride (see Interactions with other Drugs). Therefore contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

Animal toxicity

No adverse ocular or systemic effects were seen in rabbits treated topically with fixed combinations of latanoprost and timolol maleate for up to 52 weeks or with concomitantly administered latanoprost and timolol ophthalmic solutions for 4 weeks.

In long-term ocular toxicity studies in monkeys, latanoprost has been shown to induce increased iris pigmentation. The pigmentation did not progress upon discontinuation of treatment. The results from pre-clinical studies have demonstrated that the primary mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma. There is no evidence of melanocyte proliferation.

Long-term ocular administration of latanoprost at a dose of 6µg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce an increase or widening in the palpebral fissure. This effect was reversible upon discontinuation of the drug.

Timolol maleate did not produce any adverse ocular effects in rabbits and dogs, when administered as multiple daily topical doses for up to 52 and 104 weeks, respectively.

Carcinogenicity, Mutagenicity and Impaired Fertility

Carcinogenicity and mutagenicity studies with XALAPLUS have not been conducted.

Latanoprost was not carcinogenic in either rats or mice when administered by oral gavage at doses up to 170µg/kg/day for 24 and 20 months respectively.

Latanoprost was not mutagenic in gene mutation assays in bacteria and mouse lymphoma L5178Y cells and was negative in studies of unscheduled DNA synthesis. Chromosome aberrations were observed with human lymphocytes *in vitro* but latanoprost did not induce micronucleus formation *in vivo*.

No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100mg/kg/day in rats and 50mg/kg/day in mice. However, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary carcinomas were found at 500mg/kg/day. The increased incidence of mammary tumours was considered to be attributed to a species specific elevation in serum prolactin.

In vitro and *in vivo* studies with timolol maleate did not reveal a mutagenic potential.

Fertility studies with XALAPLUS have not been conducted. Latanoprost or timolol maleate alone had no effects on male or female fertility in rats when administered at 250µg/kg/day IV or 300mg/kg/day PO respectively.

Use in pregnancy (category C)

Embryofetal development studies with latanoprost have been performed in rats and rabbits. Latanoprost and/or its metabolites cross the placenta of rats. In rabbits, latanoprost caused embryofetal toxicity characterised by increased incidences of late resorption and reduced fetal weight at 5µg/kg/day IV and total litter resorption at ≥ 50µg/kg/day IV. No embryofetal effects were seen in rabbits at 1µg/kg/day IV and in rats at up to 250µg/kg/day IV.

Timolol maleate was not teratogenic in mice, rats and rabbits. Embryofetal development studies with timolol maleate in mice and rabbits showed no evidence of embryofetal toxicity at oral doses up to 50mg/kg/day. At higher doses, increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) were noted in mice (1000mg/kg/day) and increased resorption in rabbits (≥ 90mg/kg/day). In rats, delayed ossification was seen at ≥ 50mg/kg/day and a decreased number of caudal vertebral bodies and arches and an increase in hypoplastic sternebrae were noted at 500mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Therefore, XALAPLUS should not be used during pregnancy.

Use in lactation

There are limited experimental animal and no human data available on the pharmacokinetics of latanoprost in lactation. Latanoprost and its metabolites may pass into breast milk.

Timolol maleate has been detected in human milk following oral and ocular administration. Because of the potential for serious adverse reactions from XALAPLUS 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.

Use in children

XALAPLUS is not recommended for use in children. Safety and effectiveness in children have not been established.

Interactions with other drugs

No specific interaction studies have been performed with XALAPLUS.

The potential exists for additive effects resulting in hypotension, and/or marked bradycardia when timolol ophthalmic drops are administered with oral calcium channel blockers, catecholamine-depleting drugs or beta-adrenergic blocking agents, antiarrhythmics (including amiodarone and quinidine), digitalis glycosides, guanethidine[^], parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.

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.[^]

Although XALAPLUS alone has little or no effect on pupil size, mydriasis has occasionally been reported when timolol is given with adrenaline.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents (see PRECAUTIONS – Additional effects of beta-blockade).

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with benzalkonium chloride, the preservative used in XALAPLUS. If such drugs are used they should be administered with an interval of at least five (5) minutes between applications. Similarly several contact lens soaking solutions contain thiomersal (see Precautions – Use of contact lenses).

Effects on ability to drive and use of 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.

ADVERSE REACTIONS

No adverse events specific for XALAPLUS have been observed in clinical studies. The adverse events have been limited to those earlier reported for latanoprost and timolol.

Adverse events from clinical trials

Adverse events occurring at a frequency of $\geq 1\%$ in three randomised, double blind comparative trials (004, 005 and 053) are presented in Tables 1 and 2.

Table 1

Ocular adverse events (AE) that occurred in $\geq 1\%$ of patients*, in any treatment group, by preferred term†

Body system / preferred term	Number (%) of patients per treatment group		
	XALAPLUS N=394	Latanoprost N=414	Timolol N=415
Vision			
Blepharitis	10 (2.5)	10 (2.4)	7 (1.7)
Cataract	11 (2.8)	18 (4.3)	10 (2.4)
Conjunctival disorder	4 (1.0)	3 (0.7)	4 (1.0)
Conjunctivitis	12 (3.0)	11 (2.7)	13 (3.1)
Corneal disorder	12 (3.0)	11 (2.7)	14 (3.4)
Corneal ulceration	1 (0.3)*	1 (0.2)*	-
Cystoid macular oedema	1 (0.3)*	1 (0.2)*	-
Epiphora	3 (0.8)	5 (1.2)	7 (1.7)
Errors of refraction	7 (1.8)	13 (3.1)	12 (2.9)
Eye hyperaemia	29 (7.4)	40 (9.7)	12 (2.9)
Eye pain	9 (2.3)	6 (1.4)	8 (1.9)
Increased intraocular pressure	1 (0.3)	5 (1.2)	7 (1.7)
Iris pigmentation increased	6 (1.5)	13 (3.1)	4 (1.0)
Iritis	-	1 (0.2)*	2 (0.5)*
Irritation eye	49 (12.4)	54 (13.0)	29 (7.0)
Keratitis	4 (1.0)	3 (0.7)	1 (0.2)
Oedema eyelid	2 (0.5)	4 (1.0)	2 (0.5)
Photophobia	6 (1.5)	1 (0.2)	3 (0.7)
Retinal disorder	1 (0.3)	3 (0.7)	6 (1.4)
Uveitis	1 (0.3)*	-	-
Vision abnormal	26 (6.6)	29 (7.0)	22 (5.3)
Skin & Appendages			
Hypertrichosis‡	9 (2.3)	6 (1.4)	2 (0.5)
Pigmentation abnormal	1 (0.3)*	-	-
Seborrhoea	2 (0.5)	4 (1.0)	-
Skin discolouration	1 (0.3)*	-	-
Skin disorder	8 (2.0)	4 (1.0)	-
Central & Peripheral Nervous System			
Optic atrophy	2 (0.5)	3 (0.7)	6 (1.4)
Visual field defect	18 (4.6)	19 (4.6)	18 (4.3)

* Despite a low frequency of reports, some AEs are included in the listing due to the implication of a potentially sight-threatening condition.

A patient is counted only once per preferred term.

† Studies 004 and 005 included a 6 month and 053 a 12 month double-blinded period.

‡ Includes darkening, lengthening and growing of eye lashes.

Table 2:

Systemic adverse events (AE) that occurred in ≥1% of patients*, in any of the treatment groups, by body system/preferred term†

Body system / preferred term	Number (%) of patients per treatment group		
	XALAPLUS N=394	Latanoprost N=414	Timolol N=415
Respiratory			
Bronchitis	3 (0.8)	4 (1.0)	1 (0.2)
Coughing	1 (0.3)*	-	2 (0.5)*
Dyspnoea	2 (0.5)*	2 (0.5)*	2 (0.5)*
Pneumonia	1 (0.3)	3 (0.7)	4 (1.0)
Sinusitis	6 (1.5)	11 (2.7)	3 (0.7)
Upper respiratory tract infection	24 (6.1)	18 (4.3)	22 (5.3)
General			
Back pain	4 (1.0)	6 (1.4)	4 (1.0)
Chest pain	4 (1.0)	1 (0.2)	2 (0.5)
Influenza-like symptoms	10 (2.5)	4 (1.0)	3 (0.7)
Cardiovascular			
Hypertension	15 (3.8)	6 (1.4)	10 (2.4)
Hypertension aggravated	2 (0.5)*	1 (0.2)*	1 (0.2)*
Metabolic & Nutrition			
Diabetes mellitus	5 (1.3)	2 (0.5)	1 (0.2)
Diabetes mellitus aggravated	-	1 (0.2)	-
Glycosuria	2 (0.5)	1 (0.2)	-
Hyperglycaemia	1 (0.3)*	2 (0.5)*	2 (0.5)*
Hypercholesterolaemia	6 (1.5)	4 (1.0)	1 (0.2)
Central & Peripheral Nervous System			
Dizziness	2 (0.5)	4 (1.0)	1 (0.2)
Headache	9 (2.3)	15 (3.6)	5 (1.2)
Musculo-Skeletal			
Arthritis	8 (2.0)	5 (1.2)	4 (1.0)
Psychiatric			
Depression	6 (1.5)	7 (1.7)	4 (1.0)
Insomnia	1 (0.3)*	1 (0.2)*	1 (0.2)*

Body system / preferred term	Number (%) of patients per treatment group		
	XALAPLUS N=394	Latanoprost N=414	Timolol N=415
Sleep disorder	1 (0.3)	-	4 (1.0)
Skin & Appendages			
Bullous eruption	-	1 (0.2)	-
Rash	5 (1.3)	3 (0.7)	2 (0.5)
Resistance Mechanisms			
Infection	4 (1.0)	6 (1.4)	6 (1.4)
Gastro-Intestinal			
Dyspepsia	2 (0.5)	4 (1.0)	1 (0.2)
Urinary			
Cystitis	1 (0.3)	5 (1.2)	-
Urinary tract infection	1 (0.3)	2 (0.5)	4 (1.0)

* A patient is counted only once per preferred term. AEs that occurred in <1 % of the patients but were very similar to an event that did occur in ≥1% of the patients (such as “hypertension” and “hypertension aggravated”) are listed. Also, groups of mutually related AEs, where each AE may be reported in < 1%, but together they sum up to ≥1% (such as “diabetes mellitus aggravated” and “hyperglycaemia” together with “glucosuria”) are summarised.

† Studies 004 and 005 included a 6 month- and 053 a 12 month double-blinded period

The following additional adverse events have been reported with Latanoprost and Timolol eye drops:

Latanoprost:

- **Ocular:** Foreign body sensation, punctate epithelial erosions, macular oedema, corneal oedema and erosions, eyelash and vellus hair changes (increased length, thickness, pigmentation, and number)^, misdirected eyelashes sometimes resulting in eye irritation and blurred vision, photophobia^, periorbital and lid changes resulting in deepening of the eyelid sulcus^.
- **Respiratory, Thoracic and Mediastinal Disorders:** Asthma, asthma aggravation and acute asthma attacks.
- **Skin and Subcutaneous Tissue Disorders:** Darkening of the palpebral skin of the eyelids and localised skin reaction on the eyelids.
- **Musculoskeletal and Connective Tissue Disorders:** Muscle/joint pain.
- **General Disorders and Administration Site Conditions:** Non-specific chest pain^.
- **Infections and Infestations:** Herpetic keratitis^.

Timolol:

- **Special senses:** Decreased corneal sensitivity and dry eyes, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness)^, blepharitis^, keratitis^, vision blurred^, dry eyes^, corneal erosion^, diplopia, ptosis, choroidal detachment (following filtration surgery) and tinnitus.
- **Cardiovascular:** Bradycardia, arrhythmia, atrioventricular block^, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest, cardiac failure^, oedema, claudication, Raynaud's phenomenon, cold hands and feet and worsening of angina pectoris.
- **Respiratory, Thoracic and Mediastinal Disorders:** Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, pulmonary oedema and nasal congestion.
- **Body as a whole:** Asthenia and fatigue.
- **Skin and Subcutaneous Tissue Disorders:** Alopecia, pseudopemphigoid, skin rash^, and psoriasiform rash or exacerbation of psoriasis.
- **Hypersensitivity:** Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, pruritus^, localised and generalised rash.
- **Nervous system/psychiatric:** Nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia, somnolence, headache^, depression^, behavioural changes and psychiatric disturbances including confusion, hallucinations, anxiety, disorientation and nervousness.
- **Digestive:** Nausea, diarrhoea, dry mouth, dysgeusia^, vomiting^, abdominal pain^, and retroperitoneal fibrosis.
- **Metabolism and Nutrition Disorders:** Anorexia, masked symptoms of hypoglycaemia in diabetic patients.
- **Musculoskeletal and Connective Tissue Disorders:** Myalgia^.
- **Urogenital:** Decreased libido, Peyronie's disease, sexual dysfunction^, and impotence.
- **Immunologic:** Systemic lupus erythematosus.

DOSAGE AND ADMINISTRATION

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 normal.

The use of XALAPLUS may be considered in patients who require both timolol and latanoprost, but it is unknown whether patients who are adequately controlled with timolol given twice daily plus latanoprost given once daily will be as well controlled with XALAPLUS given once daily. XALAPLUS should not be used to initiate therapy.

XALAPLUS should not be given more than once daily because latanoprost is most effective at this dosage. If there is inadequate response to XALAPLUS, consideration should be given to using the individual agents with timolol dose twice daily.

If more than one topical ophthalmic drug is being used, the eye drop products should be administered at least 5 minutes apart.

Systemic absorption can be minimised by pressure on the tear duct immediately after application of the eye drop.

Use with contact lenses: The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see **PRECAUTIONS**).

OVERDOSE

There is no human data available on overdosage with XALAPLUS.

There have been reports of inadvertent overdosage with timolol-maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, hypotension, bronchospasm, and cardiac arrest.

Apart from ocular irritation and conjunctival or episcleral hyperaemia, the ocular effects of latanoprost administered at high doses are not known.

If overdosage with XALACOM occurs, treatment should be symptomatic and supportive. Studies have shown that timolol is not readily dialyzable.

If XALAPLUS is accidentally ingested the following information may be useful: One bottle contains 125µg latanoprost and 12.5mg timolol. Both timolol and latanoprost are extensively metabolised in the liver. More than 90% of latanoprost is metabolised during the first pass through the liver. Intravenous infusion of up to 3µg/kg in healthy volunteers induced no symptoms but a dose of 5.5-10µg/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.

In patients with bronchial asthma bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost. ^

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

Each 5mL bottle contains 2.5mL eye drop solution corresponding to a minimum of 80 drops of solution. One drop contains approximately 1.5µg latanoprost and 150µg timolol.

Storage

Store unopened bottle at 2^o to 8^o C.

Store opened bottle below 25^oC. Store in the outer cardboard carton. To be used within 4 weeks after opening.

Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS OF SPONSOR

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^ Please note changes in Data Sheet

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