Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codalux 50 microgram/ml + 5 mg/ml Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains latanoprost 50 micrograms and timolol maleate 6.83 mg equivalent to 5 mg timolol.

It contains 0.412 mg/ml of benzalkonium chloride solution 50%.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

The solution is a clear colourless liquid. pH 5.5 - 6.5.
Osmolality 260-320 mOsm/kg.

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

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.

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.

Use in children and adolescents

Safety and effectiveness in children and adolescents has not been established.

4.3 Contraindications

Codalux is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients.

- Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

4.4 Special warnings and precautions for use

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 and timolol 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 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, 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 documented experience in acute attacks of closed angle glaucoma. Therefore it is recommended that Codalux should be used with caution in these conditions until more experience is obtained.

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. Codalux should be used with caution in these patients.

Corneal diseases

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

Choroidal detachment

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

Systemic effects

Like other topically applied ophthalmic agents, timolol is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions 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.

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.

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.

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.

Codalux 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

Surgical anaesthesia

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving <ACTIVE substance>.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potientated 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)

Timolol may interact with other drugs, see Section 4.5.

Use of contact lenses

Codalux 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 Codalux in dry eye patients, or in conditions where the cornea is compromised. Avoid contact with soft contact lenses. Contact lenses may absorb benzalkonium chloride and these should be removed before applying Codalux but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with latanoprost and 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.

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

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 adrenergicblocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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

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.

4.6 Fertility, 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 (see Section 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 Codalux is administered until delivery, the neonate should be carefully monitored during the first days of life.

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

LACTATION

Beta-blockers are excreted into 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 4.2.

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

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 latanoprost and 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 (see Section 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.

Treatment related adverse events seen in clinical trials with latanoprost and timolol are listed below.

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

SYSTEM ORGAN CLASS	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to ≤1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Nervous System Disorders			Headache		
Eye Disorders	Increased iris pigmentation	Eye irritation (including stinging, burning and itching), Eye pain.	Eye hyperaemia, Conjunctivitis, Vision blurred, Lacrimation increased, Blepharitis, Corneal disorders.		
Skin and Subcutaneous Tissue Disorders			Skin rash, Pruritus		

Additional adverse events have been reported specific to the use of the individual components of latanoprost and timolol 50 microgram/ml + 5 mg/ml Eye Drops, Solution in either in clinical studies, spontaneous reports or in the available literature.

For latanoprost, these are:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous System Disorders:

Dizziness.

Eye Disorders:

Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), Punctate 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.

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, Connective Tissue and Bone Disorders:

Joint pain, Muscle pain.

General disorders and Administration Site Conditions:

Chest pain

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.

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with .

Therefore for timolol, these are:

Immune System Disorders:

Systemic allergic reactions including angioedema, urticaria, localized and generalized 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, 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, diplopia.

Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases).,

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.

4.9 Overdose

No data are available in humans with regard to overdose with latanoprost and timolol.

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-betablocking agents - timolol, combinations

ATC code: S01ED51

Mechanism of action

Codalux 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_{2alpha} 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

In dose finding studies, latanoprost and timolol 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 latanoprost and timolol 50 microgram/ml + 5 mg/ml eye drops, solution 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 enrolment of 5mm 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 latanoprost and timolol 50 microgram/ml + 5 mg/ml eye drops, solution, latanoprost and timolol (twice daily), respectively. The IOP lowering effect of latanoprost and timolol was maintained in 6 month open label extensions 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 Codalux 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 humour 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 eyelids.

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.

Latanoprost and timolol 50 microgram/ml + 5 mg/ml eye drops, 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 of latanoprost and timolol 50 microgram/ml + 5 mg/ml eye drops, solution 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium dihydrogen phosphate monohydrate
Disodium phosphate anhydrous
Benzalkonium chloride
Hydrochloric Acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost 50 microgram/ml eye drops, solution. If such drugs are used concomitantly with latanoprost and timolol 50 microgram/ml + 5 mg/ml eye drops, solution, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

Unopened: 3 years
Shelf life after the first opening: 28 days
Storage conditions of the product after the first opening: See section 6.4

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

Storage conditions of the product after the first opening: Do not store above 25 °C.
Use within 4 weeks.

6.5 Nature and contents of container

LDPE bottles, with an LDPE dropper applicator and a PP tamper evident cap

Each bottle contains 2.5 ml eye drop solution.

Pack sizes:

1x 2.5 ml

3x 2.5 ml

6 x 2.5ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco
Viale Amelia 70, 00181
Rome
Italy

8 MARKETING AUTHORISATION NUMBER

PA 959/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th May 2011

10 DATE OF REVISION OF THE TEXT

March 2013