PROFESSIONAL INFORMATION LEAFLET FOR CO-ATANA

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

CO-ATANA® 50 µg/ml + 5 mg/ml Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-ATANA Ophthalmic Solution contains: latanoprost 50 µg/ml and timolol maleate equivalent to 5 mg/ml timolol.
Excipient with known effect:
Preservative: Benzalkonium Chloride 0,02 % *m/v*.
For full list of excipients, see section 6.1.

3. PHARMACEUTIAL FORM

Ophthalmic solution.
Clear and colorless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are not controlled on or are intolerant to monotherapy with compounds other than latanoprost and timolol.

4.2 Posology and method of administration

Posology:

Recommended dosage for adults (including the elderly):

Recommended therapy is one drop in the affected eye(s) once daily.

If one dose is missed, treatment should continue with the next dose as planned.

Administration:

The tamper evident overcap should be removed before use.

If more than one topical ophthalmic medicine is being used, the medicines should be administered at least 5 minutes apart.

4.3 Contraindications

- CO-ATANA is contraindicated in patients with hypersensitivity to latanoprost, timolol or any other ingredient in the formulation.
- Reactive airway disease including chronic obstructive pulmonary disease, bronchial asthma or a history of bronchial asthma.
- Sinus bradycardia, second or third degree atrioventricular block, cardiogenic shock, cardiac failure.
- The safety of CO-ATANA in pregnancy has not been established (see section 4.6).
- CO-ATANA should not be used by women breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

Systemic effects:

Cardiovascular / respiratory reactions:

CO-ATANA may be absorbed systemically.

Due to the beta-adrenergic component timolol, aggravation of Prinzmetal's angina, aggravation of severe peripheral and central circulatory disorders, hypotension and bradycardia may occur.

Cardiac and respiratory reactions including death due to bronchospasm in patients with asthma and, less frequently, death associated with cardiac failure, have been reported following administration with timolol. Before treatment with CO-ATANA is initiated, cardiac failure should be adequately controlled (see section 4.3).

Anaphylactic reactions:

Patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more responsive to repeated challenge with such allergens, while taking beta-blockers, either accidental, diagnostic or therapeutic. These patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions when using CO-ATANA.

Concomitant therapy:

Timolol may have interactions with other medicines (see section 4.5).
When CO-ATANA is given to patients already receiving an oral beta-blocking agent, the effect on intraocular pressure or the known effects of systemic beta-blockade may be exaggerated. The use of two local prostaglandins or two local beta-blockers is not recommended.

Additional effects of combination products, which contain a beta-blocker:

CO-ATANA should be administered with caution in patients subjected to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving oral hypoglycaemic agents or insulin. CO-ATANA may mask the signs and symptoms associated with acute hypoglycaemia.
Treatment with CO-ATANA may mask certain symptoms of hyperthyroidism and abrupt withdrawal of therapy may precipitate a worsening of symptoms.
Treatment with CO-ATANA may aggravate symptoms of myasthenia gravis.

Ocular effects:

Latanoprost may gradually change the eye colour as a result of increasing the amount of brown pigment in the iris. This effect has predominantly been seen in patients with mixed colour irides, i.e. yellow-brown, green-brown, or blue/grey/brown and is due to the increased melanin content in the stromal melanocytes in the iris. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in the affected eyes, but parts of the iris or the entire iris may

become more brownish.

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

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

Neither freckles nor naevi 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, however, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment with CO-ATANA is instituted, patients should be made aware of the possibility of a change in eye colour. Unilateral treatment can lead to permanent heterochromia.

There is no or limited experience with latanoprost and CO-ATANA in neovascular, inflammatory, chronic angle closure or congenital glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma.

Latanoprost has little or no effect on the pupil, however there is no experience in acute attacks of closed angle glaucoma. It is therefore recommended that CO-ATANA not be used in these conditions until more experience is obtained.

Macular oedema, including cystoid macular oedema, has been reported during therapy with latanoprost. These reports have mainly occurred in patients with known risk factors for macular oedema, aphakic patients or in pseudophakic patients with a torn posterior lens capsule. In such patients CO-ATANA should be used with caution.

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

As the possibility of adverse effects on corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved

ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Use of contact lenses:

CO-ATANA contains the preservative benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should therefore be removed before instillation of the eye drops and may be reinserted after 15 minutes.

Children:

As safety and efficacy in children has not been established, CO-ATANA is not recommended for use in children.

4.5 Interaction with other medicines and other forms of interaction

No specific medicine interaction studies have been performed with CO-ATANA.
The potential exists for additive effects resulting in hypotension and/or marked bradycardia when eye drops containing timolol are administered with calcium-channel blockers, catecholamine-depleting medicines or beta-blocking agents, antidysrhythmics (including amiodarone and quinidine), parasympathomimetics, digoxin, monoamine oxidase (MAO) inhibitors and narcotics (see section 4.4).

Although CO-ATANA alone has little or no effect on pupil size, mydriasis has occasionally been reported when timolol is administered with epinephrine (adrenaline).

The hypoglycaemic effect of anti-diabetic agents may be increased by beta-blockers.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of CO-ATANA in pregnancy has not been established (see section 4.3).

Lactation:

CO-ATANA should not be used in women breastfeeding their infants, or breastfeeding should be stopped as latanoprost and its metabolites may pass into breast milk, and timolol is excreted into breast milk (see section 4.3).

4.7 Effects on ability to drive and use machines:
Instillation of CO-ATANA eye drops may cause transient blurring of vision.

4.8 Undesirable effects

The adverse effects of CO-ATANA are similar to those reported earlier for latanoprost and timolol. Based on evidence from consecutive photographs, increased iris pigmentation was observed in 16 to 20 % of all patients who received CO-ATANA eye drops for up to one year.

The most frequent findings of increased iris pigmentation were in patients with yellow-brown, green-brown and blue/grey/brown irides. In patients with homogenously grey, green, blue, or brown eyes, the change was only less frequently seen. Thickening, lengthening and darkening of the eye lashes have been reported.

The most frequently reported undesirable effects in clinical trials were irritation of the eye including stinging, burning and itching, eye hyperaemia, blepharitis, corneal disorders, conjunctivitis, eye pain, headache and skin rash.

Additional adverse events that have been seen with one of the components and may occur during treatment with CO-ATANA:

Latanoprost:	
Eye disorders:	
Frequent:	Foreign body sensation, punctate epithelial erosions.
Less frequent:	Macular oedema/cystoid macular oedema, iritis/uveitis, corneal oedema and erosions.
Respiratory, thoracic and mediastinal disorders:	
Less frequent:	Dyspnoea, asthma and asthma exacerbation.
Skin and subcutaneous tissue disorders:	
Less frequent:	Darkening of the skin on eyelids.

Timolol:	
Immune system disorders:	
Less frequent:	Symptoms of allergic reactions including angioedema, localised and generalised rash, urticaria, systemic lupus erythematosus.
Psychiatric disorders:	
Less frequent:	Nightmares, depression, memory loss.
Nervous system disorders:	
Less frequent:	Dizziness, insomnia, increase in signs and symptoms of myasthenia gravis, paraesthesia.
Eye disorders:	
Frequent:	Signs and symptoms of ocular irritation, dry eyes, keratitis, decreased corneal sensitivity.
Less frequent:	Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis and choroidal detachment (following filtration surgery).
Ear and labyrinth disorders:	
Less frequent:	Tinnitus.
Cardiac disorders:	

Less frequent:	Dysrhythmia, heart block, congestive heart failure, palpitation, cardiac arrest.
Vascular disorders:	
Less frequent:	Bradycardia, hypotension, cold hands and feet, claudication, oedema, cerebral ischaemia, Raynaud's phenomenon, cerebrovascular accident, syncope.
Respiratory, thoracic and mediastinal disorders:	
Less frequent:	Respiratory failure, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough.
Skin and subcutaneous tissue disorders:	
Less frequent:	Psoriasiform rash or exacerbation of psoriasis, alopecia.
Reproductive system and breast disorders:	
Less frequent:	Peyronie's disease, decreased libido.
General disorders and administrative site conditions:	
Less frequent:	Fatigue, chest pain, asthenia.

4.9 Overdose

There is no data available in humans with respect to overdosage with CO-ATANA.
Apart from conjunctival hyperaemia and ocular irritation, no other ocular or systemic side effects are known should overdosage with latanoprost occur. Symptoms of systemic timolol overdosage are hypotension, bradycardia, bronchospasm and cardiac arrest.
Should such symptoms occur, the treatment should be symptomatic and supportive. In studies performed, it was observed that timolol does not dialyse readily. Should CO-ATANA be accidentally ingested, the following may be useful: during the first pass through the liver, latanoprost is extensively metabolised.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.15.4 Ophthalmic preparations, other.

5.1 Pharmacodynamic properties

CO-ATANA consists of two components, latanoprost and timolol maleate, which decrease elevated intraocular pressure (IOP) by different mechanisms of action.

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a prostanoid selective prostaglandin F_2 (FP) receptor agonist that increases the outflow of aqueous humour, to reduce IOP. Increased uveoscleral outflow is the main mechanism of action. In addition, some increase in outflow activity (decrease to trabecular outflow resistance) has been reported in man.

Latanoprost has no significant effect on the production of aqueous humour, intraocular blood circulation or the blood-aqueous barrier. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term therapy.

Timolol is a non-selective beta-1 and beta-2 adrenergic receptor blocking agent. Timolol lowers IOP by reducing aqueous humour formation in the ciliary epithelium. The exact mechanism of action has not been clearly established.

5.2 Pharmacokinetic properties

Latanoprost:

Latanoprost is an inactive isopropyl ester prodrug, but following hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea. All the prodrug 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 30 ng/ml, is reached about 2 hours following topical administration of latanoprost alone.

The acid of latanoprost has a plasma clearance of 0,4 l/h/kg and a small volume of distribution of 0,16 l/kg, resulting in a rapid plasma half-life of 17 minutes.

Practically no metabolism of the acid of latanoprost occurs in the eye. Metabolism occurs mainly in the liver. The main metabolites, the 1,2,3,4-tetranor and 1,2-dinor 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 achieved about one hour after topical administration of the eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/ml is reached 10 to 20 minutes following topical administration of one eye drop to each eye once daily (300 µg/day). Half-life in plasma is about 4 hours. Timolol is extensively metabolised in the liver and the metabolites are excreted in the urine together with some unchanged timolol.

No pharmacokinetic interactions between latanoprost and timolol were observed, although there is a tendency for increased concentrations of the acid of latanoprost in aqueous humour 1 to 4 hours after administration of latanoprost and timolol compared to monotherapy. Onset of action is within one hour and maximal effect occurs within six to eight hours. The IOP reducing effect of CO-ATANA has been shown to be present up to 24 hours post dosage after multiple treatments.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

disodium phosphate anhydrous
sodium chloride
sodium dihydrogen phosphate monohydrate
water for injection
Preservative: 0,02 % *m*/v benzalkonium chloride.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 2 years
Do not use more than 30 days after opening.

6.4 Special precautions for storage

Store in a refrigerator (2 to 8 °C) in the original carton.
Once opened store at room temperature up to 25 °C.
After opening, the bottle must be stored in the original carton to protect it from light.
Do not use more than 30 days after opening.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CO-ATANA ophthalmic solution is supplied in a white sterile dropper bottle with a white sterile dropper and a white sterile cap. Each bottle contains 2,5 ml ophthalmic solution. The dropper bottle is contained in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]
Unit 7, Royal Palm Business Estate
646 Washington Street, Halfway House, Midrand, 1685
Gauteng

8. REGISTRATION NUMBER

47/15.4/0528

9. DATE OF FIRST AUTHORISATION

28 April 2016

10. DATE OF REVISION OF THE TEXT

06 July 2022

[1] Company Registration number: 2009/009360/07

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