PROFESSIONAL INFORMATION

OCUDOR CO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OCUDOR CO eye drop solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of sterile solution contains dorzolamide hydrochloride, equivalent to dorzolamide 20 mg and timolol maleate equivalent to timolol 5,0 mg.

OCUDOR CO contains benzalkonium chloride 0,0075 % *m/v* as preservative.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Ophthalmic solution

Clear, slightly viscous, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OCUDOR CO is indicated in the treatment of elevated intraocular pressure in patients with:

- ocular hypertension
- open-angle glaucoma
- pseudoexfoliative glaucoma and other secondary open-angle
- glaucomas when concomitant therapy is appropriate.

4.2 Posology and method of administration

Posology

The recommended dose is one drop of OCUDOR CO in the affected eye(s) 2 times daily.

Paediatric population

Safety and efficacy in paediatric patients below the age of 2 years have not been established. Although OCUDOR CO has been used in children 2 to 6 years of age, data on safety and efficacy are insufficient to recommend a safe and effective dose.

Method of administration

When substituting OCUDOR CO for another ophthalmic anti-glaucoma medicine, discontinue the other medicine after proper dosing on one day, and start OCUDOR CO on the next day. If more than one ophthalmic medicine is being used, OCUDOR CO and the other medicines should be administered at least 10 minutes apart.

To prevent contamination of the dropper tip and solution and to avoid eye injury, patients should be instructed not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the dispenser.

4.3 Contraindications

- Hypersensitivity to dorzolamide, timolol or to any of the ingredients of OCUDOR CO (see section 6.1)
- bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock
- pregnancy and lactation (see section 4.6).
- severe renal impairment (CrCl < 30 mL/min) or hypochloraemic acidosis
- OCUDOR CO contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses, therefore, OCUDOR CO should not be administered while wearing these contact lenses. The contact lenses should be removed before application of the drops and not

to be reinserted earlier than 15 minutes after use (see section 4.4).

The above are based on the components and are not unique to the combination.

4.4 Special warnings and precautions for use

Cardiovascular/Respiratory reactions

OCUDOR CO is absorbed systemically. Timolol is a beta-blocker, therefore the same types of adverse reactions found with systemic administration of beta-blockers may occur with OCUDOR CO. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and in some cases death in association with cardiac failure, have occurred following administration of OCUDOR CO (see section 4.3). OCUDOR CO should be used with caution in patients with mild to moderate chronic obstructive pulmonary disease (COPD).

Cardiac disorders

Patients with a history of severe cardiac disease (e.g. cardiac failure, coronary heart disease, Prinzmetal’s angina) and patients receiving beta-blocker therapy for hypertension, should be adequately controlled before beginning therapy with OCUDOR CO. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and adverse reactions.

Due to its negative effect on conduction time, OCUDOR CO should 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 given OCUDOR CO with caution.

Immunology and hypersensitivity

Dorzolamide, contained in OCUDOR CO, is a sulphonamide and although administered topically, is

absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulphonamides may occur with OCUDOR CO. Fatalities have occurred due to severe reactions to sulphonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias. Sensitisation may recur when a sulphonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of OCUDOR CO.

Local ocular adverse effects, primarily conjunctivitis and lid reactions, can occur with chronic administration of OCUDOR CO. Some of these reactions can appear as allergic-type reactions and resolve upon discontinuation of therapy. If such reactions are observed, discontinuation of treatment with OCUDOR CO should be considered.

While using OCUDOR CO, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Renal and hepatic impairment

OCUDOR CO has not been studied in patients with severe renal impairment (CL_{cr} < 30 mL/min). Since dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, OCUDOR CO is not recommended in such patients. OCUDOR CO has not been studied in patients with hepatic impairment.

Ocular

There is an increased potential for developing corneal oedema and irreversible corneal decompensation in patients with low endothelial cell counts, and in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery. Precautions should be used when prescribing OCUDOR CO to these patient groups.

Choroidal detachment has been reported with the administration of OCUDOR CO after filtration procedures.

Concomitant therapy

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition, in patients receiving an oral carbonic anhydrase inhibitor and OCUDOR CO. The concomitant administration of OCUDOR CO and oral carbonic anhydrase inhibitors is therefore not recommended.

Patients who are already receiving a beta-adrenergic blocking medicine systemically, and who are given OCUDOR CO, should be observed for a potential additive effect either on the intra- ocular pressure or on the known systemic effects of beta-blockade. The use of two beta- adrenergic blocking medicines is not recommended (see section 4.5).

Patients with phaeochromocytoma should not be given OCUDOR CO without alpha- adrenoceptor blocking therapy as well.

Withdrawal therapy

If discontinuation with OCUDOR CO is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Additional Effects of Beta-Blockade

Corneal diseases

Timolol, such as in OCUDOR CO, may induce dryness of the eyes. Patients with corneal diseases should be treated with caution.

Hypoglycaemia/diabetes

OCUDOR CO should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as timolol, such as in OCUDOR CO, may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

OCUDOR CO may also mask the signs of hyperthyroidism. Abrupt withdrawal of OCUDOR CO therapy may precipitate a worsening of symptoms.

Surgery anaesthesia

OCUDOR CO may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving OCUDOR CO.

Additional effects of carbonic anhydrase inhibition

Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with OCUDOR CO, urolithiasis has been reported infrequently. Because OCUDOR CO contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients with a prior history of renal calculi may be at increased risk of urolithiasis while using OCUDOR CO.

Other

Therapy with timolol, such as in OCUDOR CO, may aggravate myasthenia gravis.
OCUDOR CO has not been studied in patients with acute angle-closure glaucoma and should therefore not be used in this condition.

Diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilisation.

Information on excipients of OCUDOR CO

OCUDOR CO contains the preservative benzalkonium chloride, which may be absorbed by soft

contact lenses, causing eye irritation and discolouration of the contact lenses. OCUDOR CO should not be administered while wearing contact lenses. Contact lenses should be removed prior to instillation of OCUDOR CO and may be reinserted 15 minutes following administration (see section 4.3).

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preservative cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of OCUDOR CO over an extended period in patients with extensive ocular surface disease.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Paediatric population

See section 5.1

4.5 Interaction with other medicines and other forms of interaction

No specific drug interaction studies have been performed with OCUDOR CO.

There is no evidence of adverse interactions when an eye drop with timolol, such as in OCUDOR CO, is used concomitantly with the following medicines: systemic medicines, including ACE inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

Although OCUDOR CO alone has little or no effect on pupil size, mydriasis resulting from concomitant use of OCUDOR CO and epinephrine (adrenaline) may occur.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol, as in OCUDOR CO, is administered together with oral calcium channel blockers, catecholamine-depleting or beta-adrenergic blocking medicines, dysarrhythmics (including amiodarone), digoxin, parasympathomimetics, guanethidine, narcotics, and monoamine oxidase (MAO) inhibitors.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has occurred during combined treatment of CYP2D6 inhibitors (e.g. quinidine, selective serotonin reuptake inhibitors such as fluoxetine, paroxetine) and OCUDOR CO.

Timolol, such as in OCUDOR CO, may increase the hypoglycaemic effect of antidiabetic medicines.

Timolol, such as in OCUDOR CO, may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

4.6 Fertility, pregnancy and lactation

The safety of OCUDOR CO in pregnant and lactating women has not been established (see section 4.3).

Pregnancy

OCUDOR CO is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is not known whether dorzolamide hydrochloride is excreted in human milk. Timolol maleate does appear in human milk. Because of the potential for serious adverse reactions on the nursing infant, a decision should be made whether to discontinue nursing or discontinue OCUDOR CO.

Fertility

There is no data on fertility with OCUDOR CO.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Possible side effects such as blurred vision, dizziness and syncope which may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The table below reflects the adverse effects as reported with OCUDOR CO or one of its components, either during clinical studies or during post-marketing experience.

Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders *Dorzolamide hydrochloride*	Less frequent	Agranulocytosis, aplastic anaemia and other blood dyscrasias
Timolol maleate	Less frequent Frequency unknown	Systemic lupus erythematosus, agranulocytosis Increase in antinuclear antibodies, non-thrombocytopenic purpura, thrombocytopenia, transient eosinophilia

Immune system disorders *OCUDOR CO*	Less frequent	Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis
Dorzolamide hydrochloride	Less frequent	Hypersensitivity: Signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including angioedema, pruritus and urticaria, rash, shortness of breath, bronchospasm
Timolol maleate	Less frequent	Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash
Metabolism and nutrition disorders *Timolol maleate*	Frequency unknown	Hypoglycaemia, hyperglycaemia
Psychiatric disorders *Timolol maleate*	Less frequent Frequency unknown	Depression*, insomnia*, memory loss, nightmares* Hallucinations, confusion
Nervous system disorders *Dorzolamide hydrochloride*	Frequent Less frequent	Headache* Dizziness*, paraesthesia*

Timolol maleate	Frequent Less frequent	Headache* Cerebrovascular accident*, decreased libido*, dizziness*, increase in signs and symptoms of myasthenia gravis, paraesthesia*, syncope*, cerebrovascular ischaemia
Eye disorders *OCUDOR CO*	Frequent	Blurred vision, burning and stinging, conjunctival injection, corneal erosion, ocular itching, tearing
Dorzolamide hydrochloride	Frequent Less frequent Frequency unknown	Blurred vision, burning and stinging eyes, conjunctivitis, eyelid inflammation*, eyelid irritation*, eye itching, superficial punctuate keratitis, tearing Choroidal detachment following filtration surgery*, corneal oedema, eyelid crusting, iridocyclitis*, irritation including redness*, ocular hypotony, pain*, transient myopia (which resolved on therapy discontinuation)* Foreign body sensation in the eye

Timolol maleate	Frequent Less frequent Frequency unknown	Signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, dry eyes*, conjunctivitis Ptosis, diplopia, choroidal detachment (following filtration surgery)*, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)* Itching, tearing, redness, sore eyes, blurred vision, corneal erosion
Ear and labyrinth disorders *Timolol maleate*	Less frequent	Tinnitus*
Cardiac disorders *Timolol maleate*	Less frequent Frequency unknown	Bradycardia*, cardiac arrest*, chest pain*, congestive heart failure*, dysrhythmia*, heart block, palpitations* Atrioventricular block, cardiac failure
Dorzolamide hydrochloride	Frequency unknown	Palpitations, tachycardia

Vascular disorders *Timolol maleate*	Less frequent	Cerebral ischaemia, claudication, cold hands and feet*, hypotension*, oedema, Raynaud's phenomenon*, syncope
Dorzolamide hydrochloride	Frequency unknown	Hypertension
Respiratory, thoracic and mediastinal disorders *OCUDOR CO*	Frequent Less frequent	Sinusitis Respiratory failure, shortness of breath, rhinitis, bronchospasm
Dorzolamide hydrochloride	Less frequent	Epistaxis*
Timolol maleate	Less frequent Frequency unknown	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, cough*, dyspnoea*, respiratory failure Pneumonitis, pulmonary fibrosis, pleurisy
Gastrointestinal disorders *OCUDOR CO*	Frequent	Dysgeusia, taste perversion
Dorzolamide hydrochloride	Frequent Less frequent	Bitter taste, nausea* Dry mouth*, throat irritation

Timolol maleate	Less frequent Frequency unknown	Diarrhoea, dry mouth*, dyspepsia*, nausea* Abdominal cramps and pain, constipation, dysgeusia, retroperitoneal fibrosis, sclerosing peritonitis, vomiting
Hepatobiliary disorders *Dorzolamide hydrochloride*	Less frequent	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders *OCUDOR CO*	Less frequent	Contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis
Dorzolamide hydrochloride	Less frequent	Rash*, Stevens-Johnson syndrome, toxic epidermal necrolysis
Timolol maleate	Less frequent Frequency unknown	Alopecia*, psoriasiform rash or exacerbation of psoriasis* Excess sweating, pruritus, skin rash
Musculoskeletal, connective tissue and bone disorders *Timolol maleate*	Less frequent Frequency unknown	Systemic lupus erythematosus Arthralgia and myopathies including muscle cramps, myalgia

Renal and urinary disorders *OCUDOR CO*	Less frequent	Urolithiasis
Dorzolamide hydrochloride	Less frequent	Urolithiasis
Reproductive system and breast disorders *Timolol maleate*	Less frequent Frequency unknown	Peyronie's disease*, decreased libido Sexual dysfunction, male impotence
General disorders and administrative site conditions *Dorzolamide hydrochloride*	Frequent	Asthenia/fatigue*
Timolol maleate	Less frequent	Asthenia/fatigue*
Investigations *Timolol maleate*	Frequency unknown	Changes in blood concentrations of triglycerides and cholesterol, raised liver enzymes

*These adverse reactions were also observed during post-marketing experience.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP

(Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of OCUDOR CO.

Signs and symptoms:

There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest, convulsions and coma. The most common signs and symptoms to be expected with overdosage of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects (see section 4.8).

Only limited information is available with regard to human overdose by accidental or deliberate ingestion of dorzolamide hydrochloride. With oral ingestion, somnolence has been reported. With topical application the following have been reported: nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia.

Management of overdose:

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking medicines, Timolol, combinations

ATC code: S01ED51

Pharmacological classification: A.15.4 Ophthalmological preparations. Others

Mechanism of action

OCUDOR CO is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intra-ocular pressure by reducing aqueous humor secretion but does so by a different mechanism of action.

Dorzolamide hydrochloride:

Dorzolamide hydrochloride inhibits the carbonic anhydrase (CA) enzyme found in many tissues of the body including the eye. It catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. Carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II) found primarily in red blood cells (RBCs) but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Timolol maleate:

Timolol maleate is a nonselective beta-adrenergic receptor blocking medicine and reduces intra-ocular pressure.

The combined effect of these two medicines results in additional intra-ocular pressure reduction compared to either medicine administered alone.

Paediatric population

An ophthalmic solution containing 2 % dorzolamide hydrochloride and 0,5 % timolol has been used in children 2 to 6 years of age whose intraocular pressure could not be controlled on monotherapy with a 2 % dorzolamide hydrochloride solution. However, safety and efficacy data with this solution are

insufficient to recommend a safe and effective dose.

5.2 Pharmacokinetic properties

Dorzolamide hydrochloride:

Absorption:

When topically applied, dorzolamide reaches the systemic circulation. Dorzolamide accumulates in red blood cells during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free dorzolamide in plasma are maintained.

Biotransformation:

Dorzolamide forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent substance but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33 %).

When dorzolamide was given orally to stimulate maximum systemic exposure, after long term ocular administration, steady state was reached within 13 weeks. At steady state, there is virtually no free dorzolamide or metabolite in the plasma. CA inhibition in RBCs is less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results are observed after chronic, topical administration of dorzolamide. However, elderly patients with mild to moderate renal impairment (estimated CLcr 30 to 60 mL/min) have a higher metabolite concentration in RBCs, but with no meaningful differences in CA inhibition and no directly attributable clinically significant systemic side effects.

Elimination:

Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs non-linearly, resulting in a rapid decline of concentration initially, followed by a slower elimination phase with a half-life of about 4 months.

Timolol maleate:

Following a twice daily administration of timolol maleate 0,05 % ophthalmic solution, the mean peak plasma concentration is 0,35 – 0,46 ng/mL.

Paediatric population

An ophthalmic solution containing 2 % dorzolamide hydrochloride and 0,5 % timolol maleate, as in OCUDOR CO, has been evaluated in children 2 to 6 years of age whose intraocular pressure could not be controlled with dorzolamide hydrochloride alone. However, safety and efficacy data with dorzolamide hydrochloride and timolol maleate are insufficient to recommend a safe and effective dose with OCUDOR CO in this age group.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride 0,0075 % m/v (as preservative)

Hydroxyethyl cellulose

Mannitol

Sodium citrate (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

In use: 28 days of opening.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Protect from light.

Keep dispenser tightly closed and in the carton when not in use.

Use within 28 days of opening.

6.5 Nature and contents of container

White opaque polyethylene 10 mL dispenser, with a sealed dropper tip, and cap with a tamper-proof seal ring, packed into an outer carton. Each dispenser is filled with 5 mL of solution.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

A51/15.4/0162

9. DATE OF FIRST AUTHORISATION

Date of registration: 23 November 2017

10. DATE OF REVISION OF THE TEXT

19 February 2025