PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

Cosopt® Ophthalmic Solution

Strength

20 mg dorzolamide base and 5 mg timolol base

Pharmaceutical form

Ophthalmic solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Dorzolamide hydrochloride

Timolol maleate

Quantitative declaration

Each ml of COSOPT® contains 22,26 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide base and 6,83 mg timolol maleate equivalent to 5,0 mg timolol base and 0,0075 % *m/v* benzalkonium chloride as preservative.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ophthalmic solution

Clear, colourless to nearly colourless, slightly viscous solution, with a pH between 5.5, and 5.8, and an osmolarity of 242-323 mOsM.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COSOPT® is indicated in the treatment of elevated intra-ocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other secondary open-angle glaucomas when concomitant therapy is appropriate.

4.2 Posology and method of administration

Posology

The dose is one drop of COSOPT® in the affected eye(s) two times daily.

When substituting COSOPT® for another ophthalmic antiglaucoma agent(s), discontinue the other agent(s) after proper dosing on one day, and start COSOPT® on the next day.

If another topical ophthalmic agent is being used, COSOPT® and the other agent should be administered at least ten minutes apart.

Paediatric population

Safety and efficacy in paediatric patients below the age of 2 years have not been established. Although COSOPT® has been used in children 2 to 6 years of age, however data on safety and efficacy are insufficient to recommend a safe and effective dose (see Paediatric Use Section 5.1).

4.3 Contraindications

COSOPT® is contraindicated in patients with:

- reactive airway disease, including bronchial asthma or 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, overt cardiac failure, cardiogenic shock;

- severe renal impairment (CrCl < 30 ml/min) or hyperchloraemic acidosis;
- hypersensitivity to one or both active substances or to any of the excipients listed in section 6.1.

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

COSOPT® contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, COSOPT® should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use (see section 4.4.)

Pregnancy

There are no adequate and well-controlled studies in pregnant women.

4.4 Special warnings and precautions for use

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 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.

Cardiovascular / Respiratory Reactions

COSOPT® may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of cardiovascular, pulmonary or other adverse reactions found with systemic administration of beta-blockers may occur with COSOPT®. Incidence of systemic ADRs after topical administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac Disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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. COSOPT® 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.

Hepatic Impairment

COSOPT® has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Immunology and Hypersensitivity

COSOPT® may be absorbed systemically. The dorzolamide component is a sulfonamide. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with COSOPT® including severe reactions such as Stevens-

Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide hydrochloride ophthalmic solution. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of therapy. Similar reactions have been reported with COSOPT®. If such reactions are observed, discontinuation of treatment with COSOPT® should be considered.

While taking beta-blockers, including timolol, 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 used to treat anaphylactic reactions.

Concomitant Therapy

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving oral and topical carbonic anhydrase inhibitors concomitantly. The concomitant administration of COSOPT® and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given COSOPT® 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 topical beta-adrenergic blocking agents is not recommended.

Withdrawal of Therapy

As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Additional Effects of Beta-Blockade

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. Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases

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

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol. Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

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 this medicinal product, urolithiasis has been reported infrequently. Because COSOPT® 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 this medicinal product.

Use in the Elderly

Of the total number of patients in clinical studies of COSOPT®, 49 % were 65 years of age and over, while 13 % were 75 years of age and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. COSOPT® has not been studied in patients with acute angle-closure glaucoma.

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

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing COSOPT® to this group of patients.

As with the use of other antiglaucoma medicines, 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 stabilization.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with COSOPT®.

In clinical studies, COSOPT® was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel

blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g. estrogen, insulin, thyroxine).

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting drugs ~~or~~ beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine, 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, selective serotonin re-uptake inhibitors) and timolol.

Although COSOPT® alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

COSOPT® should not be used during pregnancy.

The safety of this medicine in pregnant and lactating woman has not been established (see section 4.3).

Dorzolamide

No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effect at maternotoxic doses (see section 5.3).

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 section 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 this medicinal product is administered until delivery, the neonate should be carefully monitored during the first days of life.

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 the product.

4.7 Effects on ability to drive and use machines

There are side effects associated with COSOPT® that may affect your ability to drive and/or operate machinery (see section 4.8).

4.8 Undesirable effects

During clinical studies, 1 035 patients were treated with COSOPT®. Approximately 2,4 % of all patients discontinued therapy with COSOPT® because of local ocular adverse reactions, approximately 1,2 % of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity.

The following adverse reactions have been reported with COSOPT® or one of its components either during clinical trials or during post-marketing experience:

[Very Common: (≥ 1/10), Common: (≥ 1/100, < 1/10), Uncommon: (≥ 1/1 000, < 1/100), Rare: (≥ 1/10 000, < 1/1 000) and Not Known** (cannot be estimated from the available data)]

*Adverse reactions marked with an asterisk (*) were also observed with COSOPT® during post-marketing experience.

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
Cosopt®				signs and symptoms of systemic allergic reactions, including angioedema, urticaria, rash, anaphylaxis	
Timolol maleate ophthalmic solution				signs and symptoms of allergic reactions including angioedema, urticaria, localised and generalised	pruritus

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
				rash, anaphylaxis	
Metabolism and nutrition disorders					
Timolol maleate ophthalmic solution					hypoglycaemia
Psychiatric disorders					
Timolol maleate ophthalmic solution			depression*	Insomnia*, nightmares*, memory loss	hallucination
Nervous system disorders					
Dorzolamide hydrochloride ophthalmic solution		headache*		dizziness*, paraesthesia*	
Timolol maleate ophthalmic solution		headache*	dizziness*, syncope*	paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*,	

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
				cerebrovascular accident*, cerebral ischaemia	
Eye disorders					
COSOPT®	burning and stinging	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing			
Dorzolamide hydrochloride ophthalmic solution		eyelid inflammation*, eyelid irritation*, superficial punctuate keratitis	Iridocyclitis*	irritation including redness*, pain*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal	foreign body sensation in eye

Formulation	Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)	Rare (≥ 1/10,000 to <1/1000)	Not Known**
Immune System disorders					
				detachment (following filtration surgery)*, signs and symptoms of local reactions including palpebral reaction	
Timolol maleate ophthalmic solution		signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, dry eyes, conjunctivitis	visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*	ptosis, diplopia, choroidal detachment following filtration surgery* (see Special warning and precautions for use 4.4)	itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders					
Timolol maleate ophthalmic solution				tinnitus*	

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
Cardiac disorders					
Timolol maleate ophthalmic solution			bradycardia*	chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block	atrioventricular block, cardiac failure
Dorzolamide hydrochloride ophthalmic solution					palpitations
Vascular disorders					
Timolol maleate ophthalmic solution				hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*	
Respiratory, thoracic, and mediastinal disorders					
COSOPT®		sinusitis		shortness of breath, respiratory	

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
				failure, rhinitis, bronchospasm	
Dorzolamide hydrochloride ophthalmic solution				epistaxis*	
Timolol maleate ophthalmic solution			dyspnoea*	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*	
Gastro-intestinal disorders					
COSOPT®	dysgeusia				
Dorzolamide hydrochloride ophthalmic solution		nausea*		throat irritation, dry mouth*	
Timolol maleate ophthalmic solution			nausea*, dyspepsia*	diarrhoea, dry mouth*	dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders					

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
COSOPT®				contact dermatitis*, Stevens-Johnson syndrome, toxic epidermal necrolysis	
Dorzolamide hydrochloride ophthalmic solution				rash*	
Timolol maleate ophthalmic solution				alopecia*, psoriasiform rash or exacerbation of psoriasis*	skin rash
Musculoskeletal and connective tissue disorder					
Timolol maleate ophthalmic solution				systemic lupus erythematosus	myalgia
Renal disorders					
COSOPT®			urolithiasis		
Reproductive system and breast disorders					

Formulation	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1000)	**Not Known****
Immune System disorders					
Timolol maleate ophthalmic solution				Peyronie's disease*, decreased libido	sexual dysfunction
General disorders and administration site disorders					
Dorzolamide hydrochloride ophthalmic solution		asthenia / fatigue*			
Timolol maleate ophthalmic solution			asthenia / fatigue*		

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

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

Laboratory Findings

COSOPT® was not associated with clinically meaningful electrolyte disturbances.

Reporting of side effects

If you get side effects, talk to your doctor or, pharmacist or nurse. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online

under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of COSOPT®.

Alternatively report to the following e-mail address: ZADrugsafety@mundipharma.co.za

4.9 Overdose

No data is available with regard to human overdosage by accidental or deliberate ingestion of COSOPT®.

Symptoms

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, bronchospasm, and cardiac arrest. 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 underisable effects).

Only limited information is available with regard to human overdosage 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.

Treatment

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

A.15.4 Ophthalmic preparations, other.

ATC Code: S01ED51

MECHANISM OF ACTION

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

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. 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. Timolol maleate is a nonselective beta-adrenergic receptor blocking agent and reduces intra-ocular pressure. The combined effect of these two agents results in additional intra-ocular pressure reduction compared to either component 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

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, agent and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result

of selective binding to CA-II while low concentrations of free drug in plasma are maintained. The parent agent forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent agent 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 %). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

Timolol Maleate

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0,5 %. The mean peak plasma concentration following morning dosing was 0,46 ng/ml and following afternoon dosing was 0,35 ng/ml.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established.

Dorzolamide

In rabbits given maternotoxic doses of dorzolamide associated with metabolic acidosis, malformations of the vertebral bodies were observed.

Timolol

Animal studies have not shown teratogenic effect. Furthermore, no adverse ocular effects were seen in animals treated topically with dorzolamide hydrochloride and timolol maleate ophthalmic solution or with concomitantly-administered dorzolamide hydrochloride and

timolol maleate. *In vitro* and *in vivo* studies with each of the components did not reveal a mutagenic potential. Therefore, no significant risk for human safety is expected with therapeutic doses of COSOPT®.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Benzalkonium chloride, Hydroxyethyl cellulose, mannitol, sodium citrate (dihydrate), sodium hydroxide and water for injection.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 ºC. Protect from light.

DO NOT USE MORE THAN 30 DAYS AFTER OPENING.

6.5 Nature and contents of container

COSOPT® Ophthalmic Solution is available in containers containing 5 ml solution.

The OCUMETER™ Plus Ophthalmic Dispenser consists of a translucent, high density polyethylene container with a sealed dropper tip, a flexible fluted side area which is depressed to dispense the drops, and a 2-piece cap assembly. The opaque, white, 2-piece cap mechanism punctures the dropper tip seal upon initial use, then locks to provide a single

cap during the usage period. Tamper evidence is provided by a safety strip on the container label.

COSOPT® Ophthalmic Solution is a clear, colourless to nearly colourless, slightly viscous solution.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square,

Park Lane, Century City,

Cape Town, 7441,

South Africa

8 REGISTRATION NUMBERS

South Africa S3:

32/15.4/0525

Namibia NS2:

04/15.4/1161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 October 1999

10 DATE OF REVISION OF THE TEXT

20 November 2021

COSOPT® (R): COSOPT is a Registered Trademark of Mundipharma.

OCUMETER™ (TM): OCUMETER is a Trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A., used under license.