PACKAGE INSERT
Sterile Ophthalmic Solution

COSOPT®

(dorzolamide hydrochloride and timolol maleate ophthalmic solution)

Santen

I. THERAPEUTIC CLASS

COSOPT® Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate) is the first combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

II. CLINICAL PHARMACOLOGY

IIa. Mechanism of Action

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

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor 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 that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone.

Following topical administration, COSOPT reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. COSOPT reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

IIb. Pharmacokinetics / Pharmacodynamics

Dorzolamide Hydrochloride

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the drug to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in intraocular pressure (IOP) without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug 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 extremely low concentrations of free drug in plasma are maintained. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug 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.

When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free drug or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 mL/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

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.

III. INDICATIONS

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

IV. DOSAGE AND ADMINISTRATION

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.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in an increase in local activity.

V. 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 not controlled with pacemaker, overt cardiac failure, cardiogenic shock
- severe renal impairment (CrCl<30mL/min) or hyperchloraemic acidosis
- hypersensitivity to any component of this product

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

VI. PRECAUTIONS

As with other topically-applied ophthalmic agents, this drug may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of beta-blockers may occur with topical administration. Incidence of systemic ADRs after topical administration is lower than for systemic administration.

Cardio-Respiratory Reactions

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 be given with caution to patients with first degree heart block.

Respiratory reactions including death due to bronchospasm in patients with asthma have been reported following administration of timolol maleate ophthalmic solution.

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), COSOPT should be used with caution, and only if the potential benefit outweighs the potential risk.

Vascular Disorders

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

Hepatic Impairment

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

Immunology and Hypersensitivity

As with other topically-applied ophthalmic agents, this drug 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 topical administration, 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 drug 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, 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 intraocular 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.

Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

Masking of Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

Corneal diseases

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

Surgical Anesthesia

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-adrenergic blocking agents 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.

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.

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 edema in patients with low endothelial cell counts. Precautions should be used when prescribing COSOPT to this group of patients.

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

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.

Contact Lens Use

COSOPT contains the preservative benzalkonium chloride, which may cause eye irritation. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use. Benzalkonium chloride is known to discolour soft contact lenses.

VII. PREGNANCY

COSOPT should not be used during pregnancy.

Dorzolamide

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

Timolol

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

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.

VIII. NURSING MOTHERS

It is not known whether dorzolamide hydrochloride is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed. Timolol maleate does appear in human 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. If treatment with COSOPT is required, then lactation is not recommended.

IX. PEDIATRIC USE

Efficacy in paediatric patients has not been established. Safety in paediatric patients below the age of 2 years has not been established.

A 3 month controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under 6 and greater than or equal to 2 years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received COSOPT in an open label phase. In this small group of patients, twice daily administration of COSOPT was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

X. DRUG INTERACTIONS

Concomitant use of omidenepag isopropyl and drugs containing timolol is cautioned.

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).

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, catecholamine-depleting medicines 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, fluoxetine, paroxetine) 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 β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

XI. SIDE EFFECTS

In clinical studies for COSOPT the observed adverse reactions have been consistent with those that were reported previously with dorzolamide hydrochloride and/or timolol maleate.

During clinical studies, 1035 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 (such as lid inflammation and conjunctivitis).

Like other topically applied ophthalmic medicines, 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.

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 to <1/10), Uncommon: (≥1/1,000 to <1/100), and Rare: (≥1/10,000 to <1/1,000), Not known (cannot be estimated from the available data)]

System Organ Class (MedDRA)	Formulation	Very Common	Common	Uncommon	Rare	Not Known**
Immune system disorders	COSOPT				signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis	
	Timolol maleate eye drops, solution				signs and symptoms of allergic reactions including angioedema, urticaria, localized and generalized rash, anaphylaxis	pruritus
Metabolism and nutrition disorders	Timolol maleate eye drops, solution					hypoglycaemia
Psychiatric disorders	Timolol maleate eye drops, solution			depression*	insomnia*, nightmares*, memory loss	haullucination
Nervous system disorders	Dorzolamide hydrochloride eye drops, solution		headache*		dizziness*, paraesthesia*	
	Timolol maleate eye drops, solution		headache*	dizziness*, syncope*	paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*, cerebral ischaemia	
Eye disorders	COSOPT	burning and stinging	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing			
	Dorzolamide hydrochloride eye drops, solution		eyelid inflammation*, eyelid irritation*	iridocyclitis*	irritation including redness*, pain*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal detachment (following filtration surgery)*	foreign body sensation in eye
	Timolol maleate eye drops, solution		signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, and dry eyes*	visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*	ptosis, diplopia, choroidal detachment (following filtration surgery)*	itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders	Timolol maleate eye drops, solution				tinnitus*	
Cardiac disorders	Timolol maleate eye drops, solution			bradycardia*	chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block	atrioventricular block, cardiac failure
	Dorzolamide hydrochloride eye drops, solution					palpitations
Vascular disorders	Timolol maleate eye drops, solution				hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*	
Respiratory, thoracic, and mediastinal disorders	COSOPT		sinusitis		shortness of breath, respiratory failure, rhinitis, rarely bronchospasm	
	Dorzolamide hydrochloride eye drops, solution				epistaxis*	dyspnoea
	Timolol maleate eye drops, solution			dyspnea*	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*	
Gastrointestinal disorders	COSOPT	dysgeusia				
	Dorzolamide hydrochloride eye drops, solution		nausea*		throat irritation, dry mouth*	
	Timolol maleate eye drops, solution			nausea*, dyspepsia*	diarrhea, dry mouth*	dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	COSOPT				contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	
	Dorzolamide hydrochloride eye drops, solution				rash*	
	Timolol maleate eye drops, solution				alopecia*, psoriasiform rash or exacerbation of psoriasis*	skin rash
Musculoskeletal and connective tissue disorders	Timolol maleate eye drops, solution				systemic lupus erythematosus	myalgia
Renal and urinary disorders	COSOPT			urolithiasis		
Reproductive system and breast disorders	Timolol maleate eye drops, solution				Peyronie's disease*, decreased libido	sexual dysfunction
General disorders and administration site conditions	Dorzolamide hydrochloride eye drops, solution		asthenia/ fatigue*			
	Timolol maleate eye drops, 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.

XII. OVERDOSAGE

No data are available with regard to human overdosage by accidental or deliberate ingestion of COSOPT.
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.
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.
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 dialyze readily.

XIII. AVAILABILITY

COSOPT is available in 5 ml bottle.
The bottle is made up of a white translucent low-density polyethylene bottle, a transparent dropper tip and a white cap.
COSOPT is a clear, colorless to nearly colorless, slightly viscous solution.

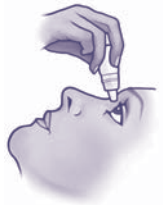
XIIIa. Storage

COSOPT Ophthalmic Solution:
Store at or below 30°C. Protect from light.
Discard one month after first opening.

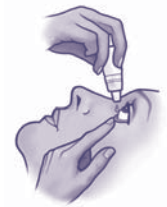
XIV. INSTRUCTIONS FOR USE

Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface. If you think your medication may be contaminated, or if you develop an eye infection, contact your doctor immediately concerning continued use of this container.
Do not use the bottle if the plastic safety strip around the neck is missing or broken. When opening the bottle for the first time, tear off the plastic safety strip.
Every time you use COSOPT:

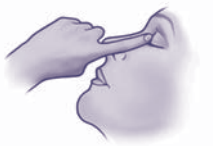
1. Wash your hands
2. Open the bottle. Take special care that the tip of the dropper bottle does not touch your eye, the skin around your eye or your fingers.
3. Tilt your head backwards and hold the bottle upside down over the eye.



4. Pull the lower eyelid downwards and look up. Gently squeeze the bottle and let one drop fall into the space between the lower eyelid and the eye.



5. Press a finger into the corner of your eye, by the nose, or close your eyelids for 2 minutes. This helps to stop the medicine from getting into the rest of the body.



6. Repeat steps 3 to 5 with the other eye if instructed to do so by your doctor.
7. Put the cap back on and close the bottle tightly.

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