

COSOPT®-S Ophthalmic Solution

(Dorzolamide 20mg/ml and Timolol 5mg/ml)

1. NAME OF THE MEDICINAL PRODUCT

COSOPT-S Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 22.26 mg of dorzolamide hydrochloride corresponding to 20 mg dorzolamide and 6.83mg of timolol maleate corresponding to 5 mg timolol.

One drop (about 0.03-0.05 mL) contains on average 0.8 mg of dorzolamide and 0.2 mg of timolol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution, single dose container

Clear, colourless to nearly colourless, slightly viscous solution, with a pH between 5.5 and 5.8, and an osmolality/freezing point depression of -0.60 to -0.45°C.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COSOPT-S is indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension and open-angle glaucoma when concomitant therapy is appropriate.

4.2 Posology and method of administration

Posology

The dose is one drop of COSOPT-S in the (conjunctival sac of the) affected eye(s) two times daily.

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

This medicinal product is a sterile solution that does not contain a preservative. The solution from one individual single dose container is to be used immediately after opening for administration to the affected eye(s). Since sterility cannot be maintained after the individual single dose container is opened, any remaining contents must be discarded immediately after administration.

Patients should be instructed to wash their hands before use and avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye (see instructions for use).

Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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

Instructions for use

Patients should be informed of the correct handling of the single-dose container. Please see section 6.5 for specific diagrams and instructions for use.

Paediatric population

Efficacy in paediatric patients has not been established.

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

4.3 Contraindications

COSOPT-S 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 ($\text{CrCl} < 30 \text{ ml/min}$) 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.

4.4 Special warnings and precautions for use

Cardiovascular/Respiratory Reactions

Like other topically applied ophthalmic agents timolol is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 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-S 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

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

Immunology and Hypersensitivity

As with other topically-applied ophthalmic agents, this medicinal product may be absorbed systemically. Dorzolamide contains a sulfonamido group, which also occurs in sulfonamides. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, 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.

Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with this medicinal product. If such reactions occur, discontinuation of COSOPT-S 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 repeated challenge with such allergens and may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant Therapy

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

The use of dorzolamide and oral carbonic anhydrase inhibitors 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 COSOPT (preserved formulation), urolithiasis has been reported infrequently. Because COSOPT-S 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. This medicinal product 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 oedema in patients with low endothelial cell counts. Precautions should be used when prescribing COSOPT-S to these groups 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.

Contact Lens Use

This medicinal product has not been studied in patients wearing contact lenses.

Paediatric population

See section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Specific medicine interaction studies have not been performed with COSOPT-S.

In a clinical study, this medicinal product was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines 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 (preserved formulation) 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.

Frequency of ocular inflammatory adverse reactions including conjunctival hyperemia was elevated in a clinical trial with concomitant administration of omidenepag isopropyl and timolol maleate. Therefore, concomitant use of omidenepag isopropyl with timolol maleate should be done with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

COSOPT-S 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 (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.

Breast-feeding

It is not known whether dorzolamide is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed.

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce systemic absorption, see section 4.2. If treatment with COSOPT-S is required, then lactation is not recommended.

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 may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects

In a clinical study for COSOPT-S (preservative-free) the observed adverse reactions have been consistent

with those that were reported previously with COSOPT (preserved formulation), dorzolamide hydrochloride and/or timolol maleate.

During clinical studies, 1035 patients were treated with COSOPT (preserved formulation). Approximately 2.4% of all patients discontinued therapy with COSOPT (preserved formulation) 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).

COSOPT-S (preservative-free) has been shown to have a similar safety profile to COSOPT (preservative containing formulation) in a repeat dose double-masked, comparative study.

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-S (preservative-free) or one of its components either during clinical trials or during post-marketing experience:

[Very Common: ($\geq 1/10$), Common: ($\geq 1/100$, $< 1/10$), Uncommon: ($\geq 1/1000$, $< 1/100$), and Rare: ($\geq 1/10,000$, $< 1/1000$), Not known (cannot be estimated from the available data)]

System Organ Class (MedDRA)	Formulation	Very Common	Common	Uncommon	Rare	Not Known**
Immune system disorders	<u>COSOPT-S</u>				signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis	
	<u>Timolol maleate eye drops, solution</u>				signs and symptoms of allergic reactions including angioedema, urticaria, localized and generalized rash, anaphylaxis	pruritus
Metabolism and nutrition disorders	<u>Timolol maleate eye drops, solution</u>					hypoglycaemia
Psychiatric disorders	<u>Timolol maleate eye drops, solution</u>			depression*	insomnia*, nightmares*, memory loss	hallucination
Nervous system disorders	<u>Dorzolamide hydrochloride eye drops, solution</u>		headache*		dizziness*, paraesthesia*	

	<u>Timolol maleate eye drops, solution</u>		headache*	dizziness*, syncope*	paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*, cerebral ischaemia	
Eye disorders	<u>COSOPT-S</u>	burning and stinging	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing			
	<u>Dorzolamide hydrochloride eye drops, solution</u>		eyelid inflammation*, eyelid irritation*	iritidocyclitis*	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
	<u>Timolol maleate eye drops, solution</u>		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* (see Special warning and precautions for use 4.4)	itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders	<u>Timolol maleate eye drops, solution</u>				tinnitus*	
Cardiac disorders	<u>Timolol maleate eye drops, solution</u>			bradycardia*	chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block	atrioventricular block, cardiac failure

	<u>Dorzolamide hydrochloride eye drops, solution</u>					palpitations
Vascular disorders	<u>Timolol maleate eye drops, solution</u>				hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*	
Respiratory, thoracic, and mediastinal disorders	<u>COSOPT-S</u>		sinusitis		shortness of breath, respiratory failure, rhinitis, rarely bronchospasm	
	<u>Dorzolamide hydrochloride eye drops, solution</u>				epistaxis*	dyspnoea
	<u>Timolol maleate eye drops, solution</u>			dyspnoea*	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*	
Gastrointestinal disorders	<u>COSOPT-S</u>	dysgeusia				
	<u>Dorzolamide hydrochloride eye drops, solution</u>		nausea*		throat irritation, dry mouth*	
	<u>Timolol maleate eye drops, solution</u>			nausea*, dyspepsia*	diarrhoea, dry mouth*	dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	<u>COSOPT-S</u>				contact dermatitis, Stevens- Johnson syndrome, toxic epidermal necrolysis	
	<u>Dorzolamide hydrochloride eye drops, solution</u>				rash*	
	<u>Timolol maleate eye drops, solution</u>				alopecia*, psoriasiform rash or exacerbation of psoriasis*	skin rash

Musculoskeletal and connective tissue disorders	<u>Timolol maleate eye drops, solution</u>				systemic lupus erythematosus	myalgia
Renal and urinary disorders	<u>COSOPT-S</u>			urolithiasis		
Reproductive system and breast disorders	<u>Timolol maleate eye drops, solution</u>				Peyronie's disease*, decreased libido	sexual dysfunction
General disorders and administration site conditions	<u>Dorzolamide hydrochloride eye drops, solution</u>		asthenia / fatigue*			
	<u>Timolol maleate eye drops, solution</u>			asthenia/ fatigue*		

*These adverse reactions were also observed with COSOPT (preserved formulation) during post-marketing experience.

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

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of COSOPT (preserved formulation) or COSOPT-S.

Symptoms

There have been reports of inadvertent overdoses 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 overdoses 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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations, ATC code: S01ED51

Mechanism of action

COSOPT-S 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. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction (IOP) compared to either component administered alone.

Following topical administration, COSOPT-S 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. This medicinal product reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

5.2 Pharmacokinetic properties

Dorzolamide Hydrochloride

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the active substance to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure.

When topically applied, dorzolamide reaches the systemic circulation. The parent active substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent active 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%). 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 active substance concentration initially, followed by a slower elimination phase with a half-life of about four months.

Timolol Maleate

In a study of plasma active substance 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethylcellulose
Mannitol
Sodium citrate
Sodium hydroxide for pH adjustment
Water for injection.

6.2 Shelf life

3 years

COSOPT-S should be used no longer than 1 month after first opening the pouch. Discard any unused single dose containers after that time.

Discard the opened single dose container immediately after first use.

6.3 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.4 Nature and contents of container

COSOPT-S is available in 0.2 ml low density polyethylene single-dose containers.

Pack sizes:
0.2 ml x 60 (3 pouches, each with 20 single-dose containers)

6.5 Special precautions for disposal and other handling

No special requirements.

Instructions for use

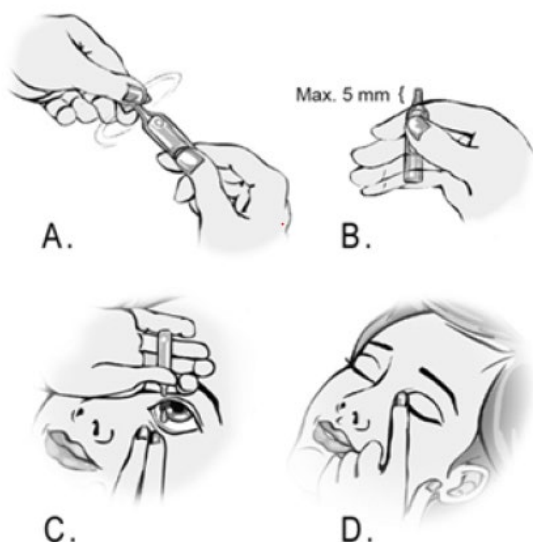
Open the foil pouch which contains the individual single-dose containers. Write the date of first opening on the pouch.

Every time you use COSOPT-S:

1. Wash your hands.
2. Take the strip of containers from the pouch.
3. Detach one single-dose container from the strip.
4. Put the remaining strip back in the pouch and fold the edge to close the pouch.
5. To open the container, twist off the tab (Picture A).
6. Hold the container between your thumb and index finger. Note that the tip of the container must not show more than 5 mm above the edge of your index finger (Picture B).

7. Tilt your head backwards or lie down. Place your hand on your forehead. Your index finger should be aligned with your eyebrow or resting on the bridge of the nose. Look up and pull the lower eyelid downward with the other hand. **Do not allow any part of the container to touch your eye or any area around your eye.** Gently squeeze the container to let one drop fall into the space between the lid and the eye (Picture C). Do not blink while applying the drop to your eye. Each single-dose container contains enough solution for both eyes.
8. Close your eye and press the inner corner of the eye with your finger for about two minutes. This helps to stop the medicine from getting into the rest of the body (Picture D).
9. Wipe off any excess solution from the skin around the eye.

If your doctor has told you to use drops in both eyes, repeat steps 7 to 9 for your other eye.



After putting the drop into the eye(s), throw away the used single-dose container even if there is solution remaining to avoid contamination of the preservative free solution.

Store the remaining containers in the foil pouch; the remaining containers must be used within 1 month after opening of the pouch. If there are any containers left 1 month after opening the pouch they should be safely thrown away and a fresh pouch should be opened. It is important to continue to use the eye drops as prescribed by your doctor.

If you are not sure how to administer your medicine, ask your doctor, pharmacist or nurse.

7. MANUFACTURER

SANTEN PHARMACEUTICAL CO., LTD.

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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION OF THE TEXT

February 2022