TRUSOPT® 2% Ophthalmic Solution

dorzolamide hydrochloride

1 Trusopt 2% Opthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1mL of TRUSOPT 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

TRUSOPT ophthalmic Solution is a sterile, isotonic, buffered, slightly viscous aqueous solution available in a 5mL translucent plastic dispensing bottle with an opaque white cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TRUSOPT Ophthalmic Solution 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
- in the short-term treatment of paediatric glaucomas as adjunctive therapy to beta-blockers and for monotherapy when other treatments have proved ineffective or are unsuitable.

4.2 Dose and method of administration

Dose

When used as monotherapy, the dose is one drop of TRUSOPT Ophthalmic Solution in the affected eye(s) three times daily.

When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of TRUSOPT in the affected eye(s) two times daily.

Paediatric population

In paediatric patients, when used as monotherapy and when used as adjunctive therapy, the dose is one drop of TRUSOPT in the affected eye(s) three times daily.

Method of administration

When substituting TRUSOPT for another ophthalmic anti-glaucoma agent, discontinue the other agent after proper dosing on one day, and start TRUSOPT on the next day.

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

4.3 Contraindications

TRUSOPT is contraindicated in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Renal impairment

TRUSOPT has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because TRUSOPT and its metabolite are excreted predominantly by the kidney, TRUSOPT is not recommended in such patients.

Acute angle-closure glaucoma

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

Hepatic impairment

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

Systemic effects

TRUSOPT 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 topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

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 TRUSOPT. The concomitant administration of TRUSOPT and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Local ocular adverse effects

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

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

TRUSOPT Ophthalmic Solution contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore, TRUSOPT should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing TRUSOPT to this group of patients.

Paediatric Use

Safety and IOP-lowering effects of TRUSOPT have been evaluated in paediatric patients <6 years of age with glaucoma or elevated intraocular pressure (baseline IOP ≥22 mmHg). Use of TRUSOPT in this age group is supported by evidence from a 3-month, double-masked, active-treatment controlled study.

Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. Patients with significant renal tubular immaturity should only receive dorzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis.

Use in the Elderly

Of the total number of patients in clinical studies of TRUSOPT, 44% were 65 years of age and over, while 10% 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 to the product cannot be ruled out.

Other Precautions

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

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

Patients should be advised that if they develop an intercurrent ocular condition (eg. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

4.5 Interaction with other medicines and other forms of interaction

Specific medicine interaction studies have not been performed with TRUSOPT Ophthalmic Solution. In clinical studies, TRUSOPT was used concomitantly with the following medications without evidence of adverse interactions: timolol ophthalmic solution, betaxolol ophthalmic solution and systemic medications, including ace-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

TRUSOPT is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, TRUSOPT was not associated with acid-base disturbances. However,

these disturbances have been reported with oral carbonic anhydrase inhibitors and have in some instances, resulted in medicine interactions (e.g. toxicity associated with high-dose salicylate therapy). Therefore, the potential for such medicine interactions should be considered in patients receiving TRUSOPT. Also see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. TRUSOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

Breastfeeding

It is not known whether this medicine is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

There are potential adverse effects of TRUSOPT that may affect some patients' ability to drive and use machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

TRUSOPT was evaluated in more than 1400 individuals in controlled and uncontrolled clinical studies. In long term studies of 1108 patients treated with TRUSOPT as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with TRUSOPT was medicine-related ocular adverse effects, primarily conjunctivitis and lid reactions (see Warnings and Precautions).

In clinical studies the most common ocular complaints were burning and stinging, blurred vision, itching and tearing. Bitter taste was also frequently reported. If these local symptoms were considered clinically important by investigators they also appear as adverse experiences in the listing below.

List of adverse reactions

Adverse experiences that were reported as medicine-related (possibly, probably, or definitely) in 1-5% of patients on TRUSOPT were, in decreasing order of frequency:

Ocular: Burning and stinging, conjunctivitis, eyelid inflammation, eye itching, eyelid irritation.

Systemic: Headache, bitter taste, nausea, asthenia/fatigue. In addition, iridocyclitis and rash were each reported rarely. Also, there was one report of urolithiasis.

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, urticaria and pruritus

Nervous System: Dizziness, paresthesia

Ocular: Pain, redness, transient myopia (which resolved upon discontinuation of therapy), superficial punctate keratitis, eyelid crusting, choroidal detachment following filtration surgery

Skin/Mucous Membranes: Contact dermatitis, epistaxis, throat irritation, dry mouth, Stevens-Johnson syndrome, toxic epidermal necrolysis

Urogential: Urolithiasis

Paediatric Patients

In a clinical trial with 184 paediatric patients the adverse event profile of dorzolamide hydrochloride was comparable to that seen in adult patients. In this trial approximately 20% of patients had a medicine-related adverse event, the majority of which were local, non serious ocular effects such as burning stinging, injection and eye pain. A small percentage of patients in this trial (<4%) were observed to have corneal oedema or haze. Local reactions appeared similar in frequency to the comparator.

In post marketing data, metabolic acidosis in the very young children particularly with renal immaturity/impairment has been rarely reported.

Laboratory Findings

TRUSOPT was not associated with clinically meaningful electrolyte disturbances.

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 asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possible central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglucoma preparations and miotics, Carbonic Anhydrase Inhibitor

ATC code: S 01 EC 03

Mechanism of action

TRUSOPT (dorzolamide hydrochloride ophthalmic solution) is a novel carbonic anhydrase inhibitor formulated for topical ophthalmic use. Unlike oral carbonic anhydrase inhibitors, TRUSOPT, which is administered topically, exerts its effects directly in the eye.

TRUSOPT Sterile Ophthalmic Solution contains dorzolamide hydrochloride, which is described chemically as: (4*S*,-*trans*) -4- (ethylamino) -5,6- dihydro -6-methyl -4H- thieno [2,3-b] thiopyran -2-sulphonamide 7,7- dioxide mono-hydrochloride. Dorzolamide hydrochloride is optically active.

The specific rotation is $\alpha 25°$(C=1, water) = ~ -17°.

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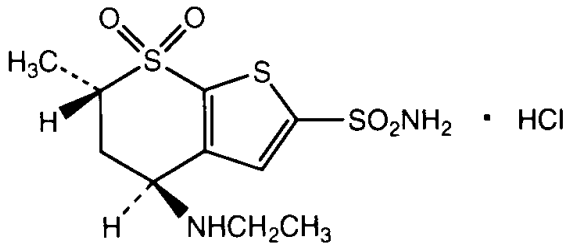
Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \bullet HCl$ and its structural formula is:



Dorzolamide hydrochloride has a molecular weight of 360.9 and a melting point of about 264°C. It is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. In humans, 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. The result is a reduction in intraocular pressure (IOP).

TRUSOPT Ophthalmic Solution contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, TRUSOPT 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. Unlike miotics, TRUSOPT reduces intraocular pressure without the common adverse effects of miotics such as night blindness, accommodative spasm and pupillary constriction. Unlike topical beta-blockers, TRUSOPT has minimal or no effect on pulse rate or blood pressure.

Topically applied beta-adrenergic blocking agents also reduce IOP by decreasing aqueous humor secretion but by a different mechanism of action. Studies have shown that when TRUSOPT is added

to a topical beta-blocker, additional reduction in IOP is observed; this finding is consistent with the reported additive effects of beta-blockers and oral carbonic anhydrase inhibitors.

Clinical efficacy and safety

In patients with glaucoma or ocular hypertension, the efficacy of TRUSOPT given t.i.d as monotherapy (baseline IOP >23 mm Hg) or given b.i.d as adjunctive therapy while receiving ophthalmic beta-blockers (baseline IOP >22 mm Hg) was demonstrated in large-scale clinical studies of up to one-year duration. The IOP-lowering effect of TRUSOPT as monotherapy and as adjunctive therapy was demonstrated throughout the day and this effect was maintained during long-term administration. Efficacy during long-term monotherapy was similar to betaxolol and slightly less than timolol. When used as adjunctive therapy to ophthalmic beta-blockers, TRUSOPT demonstrated additional IOP lowering similar to pilocarpine 2% q.i.d.

5.2 Pharmacokinetic properties

Absorption

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the medicine 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 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, medicine and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured.

Distribution and Biotransformation

Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free medicine in plasma are maintained. The parent medicine forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent medicine 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%).

Elimination

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 medicine 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 medicine 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 TRUSOPT. However, some elderly patients with renal impairment (estimated CrCl 30-60mL/min) had higher metabolite

concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic adverse effects were directly attributable to this finding.

5.3 Preclinical safety data

Animal Toxicology

The main findings in animal studies with dorzolamide administered orally were related to the pharmacological effects of systemic carbonic anhydrase inhibition. Some of these findings were species-specific and/or were a result of metabolic acidosis.

In clinical studies, patients did not develop signs of metabolic acidosis or serum electrolyte changes, which are indicative of systemic CA inhibition. Therefore, it is not expected that the effects noted in animal studies would be observed in patients receiving therapeutic doses of TRUSOPT.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethyl cellulose

Mannitol

Sodium citrate dehydrate

Sodium hydroxide (to adjust pH)

Water for injections

Benzalkonium chloride (preservative)

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store TRUSOPT Ophthalmic Solution below 30°C. Protect from light.

6.5 Nature and contents of container

A sterile, isotonic, buffered, slightly viscous aqueous solution available in a 5mL translucent plastic dispensing bottle with an opaque white cap.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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17 November 1994

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05 May 2017

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new SPC format