PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

TRUSOPT® 2 % Ophthalmic Solution

Strength

Each ml contains 20 mg dorzolamide base

Pharmaceutical form

Ophthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Dorzolamide base

Quantitative declaration

Each ml of TRUSOPT® 2 % contains 22,26 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide 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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TRUSOPT® 2 % 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
- and in the short term treatment of paediatric glaucomas as adjunctive therapy to beta-blockers and for monotherapy

4.2 Posology and method of administration

Posology

When used as monotherapy, the dose is one drop of TRUSOPT® 2 % Ophthalmic Solution in the affected eye(s) 3 times daily.

When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of TRUSOPT® 2 % in the affected eye(s) 2 times daily.

When substituting TRUSOPT® 2 % for another ophthalmic anti-glaucoma agent, discontinue the other agent after proper dosing in one day, and start TRUSOPT® 2 % on the next day. If more than one topical ophthalmic medicine is being used, the medicines should be administered at least 10 minutes apart.

4.3 Contraindications

TRUSOPT® 2 % is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

TRUSOPT® 2 % has not been studied in patients with moderate progressing to severe renal impairment (CrCl < 30 ml/min) or with hyperchloraemic acidosis. Because TRUSOPT® 2 % and its metabolite are excreted predominantly by the kidney, TRUSOPT® 2 % is not recommended in such patients.

TRUSOPT® 2 % has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

TRUSOPT® 2 % has not been studied in patients wearing contact lenses. TRUSOPT® 2 % Ophthalmic Solution contains the preservative, benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore, TRUSOPT® 2 % should not be administered while wearing soft contact lenses.

4.4 Special warnings and precautions for use

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. TRUSOPT® 2 % has not been studied in patients with acute angle-closure glaucoma.

TRUSOPT® 2 % 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 TRUSOPT® 2 %. Fatalities have occurred, although rarely, due to severe reactions to sulphonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, and other blood dyscrasias. Sensitisation may recur when a sulphonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of TRUSOPT® 2 %.

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 dorzolamide, urolithiasis has been reported infrequently.

Because dorzolamide is 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 dorzolamide.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of TRUSOPT® 2 %. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of therapy. If such reactions are observed, treatment with TRUSOPT® 2 % should be discontinued and the patient evaluated before considering restarting the medicine.

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® 2 %. The concomitant administration of TRUSOPT® 2 % and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Corneal oedemas and irreversible corneal decompensations have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery while using TRUSOPT® 2 %. TRUSOPT® 2 % should be used with caution in such patients.

There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing TRUSOPT® 2 % to this group of patients.

Choroidal detachment has been reported with the administration of TRUSOPT® 2 % after filtration procedures.

Benzalkonium chloride

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.

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

Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Contact Lens Use

TRUSOPT® 2 % contains benzalkonium chloride as preservative. Contact lenses should be removed prior to application and wait at least 15 minutes before reinsertion.

Benzalkonium chloride is known to discolour soft contact lenses.

Paediatric population

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® 2 %, 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.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with TRUSOPT® 2 % Ophthalmic Solution. In clinical studies, TRUSOPT® 2 % 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 drugs including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

Association between dorzolamide and miotics and adrenergic agonists has not been fully evaluated during glaucoma therapy.

TRUSOPT® 2 % is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, TRUSOPT® 2 % 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 interactions (e.g. toxicity associated with high-dose salicylate therapy). Therefore, the potential for such interactions should be considered in patients receiving TRUSOPT® 2 %.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are not adequate and well-controlled studies in pregnant women. TRUSOPT® 2 % should not be used during pregnancy. In rabbits given maternotoxic doses associated with metabolic acidosis ≥ 2,5 mg/kg/day, malformation of the vertebral bodies were observed (see section 5.3).

Breastfeeding

Safety during breast-feeding has not been established.

It is unknown whether dorzolamide/metabolites are excreted in human milk.

Available pharmacodynamic/toxicological data in animals have shown excretion of dorzolamide/metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from TRUSOPT® 2 % therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. A risk to the newborns/infants cannot be excluded.

Fertility

Animal data do not suggest an effect of treatment with dorzolamide on male and female fertility. Human data are lacking.

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 dizziness and visual disturbances may affect the ability to drive and use machines.

4.8 Undesirable effects

TRUSOPT® 2 % was evaluated in more than 1 400 individuals in controlled and uncontrolled clinical studies. In long term studies of 1 108 patients treated with TRUSOPT® 2 % as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3 %) from treatment with TRUSOPT® 2 % was drug-related ocular adverse effects, primarily conjunctivitis and lid reactions.

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

Body System	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not Known**
Nervous system disorders		Headache		Dizziness, paraesthesia	
Eye disorders	Burning and stinging eyes	Superficial punctate keratitis, tearing, conjunctivitis, eyelid inflammation, eye itching,	Iridocyclitis	Irritation including redness, pain, eyelid crusting, transient myopia (which resolved upon discontinuation	foreign body sensation in eye

Body System	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not Known**
		eyelid irritation, blurred vision		of therapy), corneal oedema, ocular hypotony, choroidal detachment following filtration surgery	
Cardiac disorders					Palpitations
Respiratory, thoracic, and mediastinal disorders				Epistaxis	Dyspnoea
Gastrointestinal disorders		Nausea, bitter taste		Dry mouth, throat irritation	
Skin and subcutaneous disorders				Stevens-Johnson syndrome, toxic epidermal necrolysis,	

Body System	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not Known**
				contact dermatitis	
Renal and urinary disorders				Urolithiasis	
General disorders and administration site conditions		Asthenia/fatigue		Hypersensitivity: Signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm	
Investigations					TRUSOPT® 2 % was not associated with clinically

Body System	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1 000 to <1/100)	**Rare** (≥ 1/10 000 to <1/1 000)	**Not Known**
					meaningful electrolyte disturbances.

Paediatric population

The most frequent adverse events associated with TRUSOPT® 2 % in patients younger than 2 years of age were ocular injection (5,4 %) and eye discharge (3,6 %). In patients older than 2 years of age, but younger than 6 years the most frequent adverse events associated with TRUSOPT® 2 % were burning/stinging in the eye (12,1 %), ocular injection (7,6 %), eye pain (3 %) and eyelid inflammation (3 %) (see section 5.1).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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

4.9 Overdose

Limited data are available in humans in regard to overdosage by accidental or deliberate ingestion.

Symptoms

The following have been reported with oral ingestion: somnolence; topical

application: nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia.

Treatment

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.4 Ophthalmic preparations, other.

ATC Code: S01EC03

Mechanism of Action

Dorzolamide hydrochloride, is a carbonic anhydrase inhibitor formulated for topical ophthalmic use. Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. 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, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Paediatric population

Safety and IOP-lowering effects of TRUSOPT® 2 % have been evaluated in paediatric patients younger than 6 years of age with glaucoma or elevated intraocular pressure

(baseline IOP higher than 22 mm Hg). Use of TRUSOPT® 2 % in this age group is supported by evidence from a 3 month, controlled study.

5.2 Pharmacokinetic properties

When topically applied, dorzolamide reaches the systemic circulation. Dorzolamide accumulates in red blood cells (RBCs) during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free drug in plasma are maintained. Dorzolamide forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent substance but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in red blood cells (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 agent 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 dorzolamide or metabolite in plasma. CA inhibition in red blood cells (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. However, some elderly patients with mild to moderate renal impairment (estimated CrCl 30 to 60 ml/min) had higher metabolite concentrations in red blood cells (RBCs), but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

5.3 Preclinical safety data

The main findings in animal studies with dorzolamide hydrochloride administered orally were related to the pharmacological effects of systemic carbonic anhydrase inhibition. Some of these findings were species-specific and/or were result of metabolic acidosis. In rabbits given maternotoxic doses of dorzolamide associated with metabolic acidosis, malformations of the vertebral bodies were observed. In lactating rats, decreases in the body weight gain of offspring were observed. No adverse effects upon fertility were observed in male and female rats given dorzolamide prior to and throughout mating.

In clinical studies, patients did not develop signs of metabolic acidosis or serum electrolyte changes that 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 dose of dorzolamide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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 25 °C. Protect from light.

DO NOT USE MORE THAN 30 DAYS AFTER OPENING.

6.5 Nature and contents of container

TRUSOPT® 2 % Ophthalmic Solution is supplied in Ocumeter™ containers containing 5 ml solution.

TRUSOPT® 2 % 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 NUMBER(S)

South Africa S3

29/15.4/0766

Namibia NS2

13/15.4/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 October 2014

10 DATE OF REVISION OF THE TEXT

13 December 2021

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