SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

TRUSOPT® 2 % Ophthalmic Solution

COMPOSITION

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.
Inactive ingredients: Hydroxyethyl cellulose, mannitol, sodium citrate (dihydrate), sodium hydroxide and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A.15.4 Ophthalmic preparations, other.

PHARMACOLOGICAL ACTION

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).
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 (RBC's) 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 (RBC's), but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

Summary of Clinical Studies

Paediatric use

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.

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

CONTRA-INDICATIONS

TRUSOPT® 2 % is contra-indicated in patients who are hypersensitive to any component of this product.

TRUSOPT® 2 % has not been studied in patients with moderate progressing to severe renal impairment (CrCl < 30 ml/min). 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.

WARNINGS AND SPECIAL PRECAUTIONS

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.

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 anemia, 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 %.

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.

There is an increased potential for developing corneal edema 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.

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.

INTERACTIONS

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).

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 %.

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.

Lactation

Safety during breast-feeding has not been established.

DOSAGE AND DIRECTIONS FOR USE

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.

SIDE 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.

Paediatric Patients

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 %).

The following adverse reactions have been reported in post-marketing experience:
Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100) and Rare (≥ 1/10 000, < 1/1 000)

Nervous system and psychiatric disorders

Common: Headache

Rare: Dizziness, paraesthesia

Eye Disorders

Very common: Burning and stinging eyes

Common: Superficial punctuate keratitis, tearing, conjunctivitis, eyelid inflammation, eye itching, eyelid irritation, blurred vision

Uncommon: Iridocyclitis

Rare: Irritation including redness, pain, eyelid crusting, transient myopia (which resolved upon discontinuation of therapy), corneal oedema, ocular hypotony, choroidal detachment following filtration surgery

Respiratory, thoracic and mediastinal disorders

Rare: Epistaxis

Gastrointestinal disorders

Common: Nausea, bitter taste

Rare: Dry mouth

Renal disorders

Rare: Urolithiasis

Immune system disorders

Rare: Hypersensitivity: Signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm

General disorders and administration site conditions

Common: Asthenia/fatigue

Skin disorders

Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis

Laboratory Findings

TRUSOPT® 2 % was not associated with clinically meaningful electrolyte disturbances.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

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.

IDENTIFICATION

TRUSOPT® 2 % Ophthalmic Solution is a clear, colourless to nearly colourless, slightly viscous solution.

PRESENTATION

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

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light.

Keep out of reach of children.

DO NOT USE MORE THAN 30 DAYS AFTER OPENING.

REGISTRATION NUMBER

South Africa: S3

29/15.4/0766

Namibia: NS2

13/15.4/0014

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd
Block D, Grosvenor Square,
Park Lane, Century City,
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DATE OF PUBLICATION OF THIS PACKAGE INSERT

03 October 2014 (Revision 1: 10 March 2015)

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S3

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

TRUSOPT® 2 % Ophthalmic Solution

Please read all of this leaflet carefully before you start using TRUSOPT® 2 %

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- TRUSOPT® 2 % has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT TRUSOPT® 2 % CONTAINS

TRUSOPT® 2 % is a sterile eyedrop.

TRUSOPT® 2 % contains 2 % dorzolamide hydrochloride, a sulphonamide related compound as the active ingredient.

The other ingredients are**:** Hydroxyethyl cellulose, mannitol, sodium citrate (dihydrate), sodium hydroxide and water for injection. Benzalkonium chloride is added as a preservative.

2. WHAT TRUSOPT® 2 % IS USED FOR

TRUSOPT® 2 % is prescribed to lower raised pressure in the eye in the treatment of glaucoma.

3. BEFORE YOU USE TRUSOPT® 2 %

Do not use TRUSOPT® 2 %

If you are hypersensitive (allergic) to dorzolamide or any of the other ingredients of TRUSOPT® 2 %.

Take special care with TRUSOPT® 2 %

Tell your doctor about any medical problems you currently have or have had in the past, and about any allergies to any medications.

If you suspect that TRUSOPT® 2 % is causing an allergic reaction (e.g. skin rash or itching), stop its use and contact your doctor at once.

If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your doctor immediately.

If you wear contact lenses, you should consult your doctor before using TRUSOPT® 2 %.

Use in children

TRUSOPT® 2 % has been studied in infants and children less than 6 years of age who have raised pressure in the eye(s) or have been diagnosed with glaucoma. For more information, talk to your doctor.

Use in the elderly

In studies with TRUSOPT® 2 %, the effects of TRUSOPT® 2 % were similar in both elderly and younger patients.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before taking this medicine. Your doctor will decide if you should use TRUSOPT® 2 %.

Driving and using machinery

There are side effects associated with this product that may affect your ability to drive or operate machinery (see "**POSSIBLE SIDE EFFECTS").**

Important information about some of the ingredients of TRUSOPT® 2 %

TRUSOPT® 2 % contains the preservative benzalkonium chloride. This preservative may be deposited in soft contact lenses. If you wear contact lenses consult your doctor before using TRUSOPT® 2 %.

What should I tell my doctor before using TRUSOPT® 2 %

Tell your doctor about all medicines, (including eye drops) that you are using or plan to use, including those obtained without a prescription, particularly large doses of aspirin or sulpha drugs.

Tell your doctor if you now have or have had any past kidney or liver problems.

Taking other medicines with TRUSOPT® 2 %

Always tell your healthcare professional if you are taking any other medicine.
(This includes complementary or traditional medicines).

4. HOW TO USE TRUSOPT® 2 %

Your doctor will establish the appropriate dose and duration of treatment.

When TRUSOPT® 2 % is used alone, the dose is one drop in the affected eye(s) in the morning, in the afternoon and in the evening.

Do not share medicines prescribed for you with any other person.

If your doctor has recommended you use TRUSOPT® 2 % with a beta-blocker eye drop to lower eye pressure, then the dose is one drop of TRUSOPT® 2 % in the affected eye(s) in the morning and in the evening.

If you are using TRUSOPT® 2 % with another eye drop, the drops should be instilled at least 10 minutes apart.

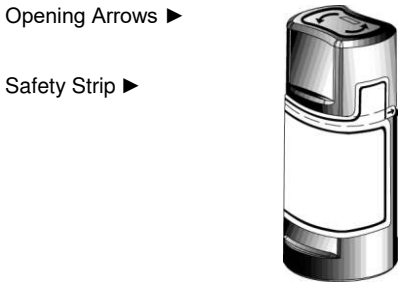
Do not allow the tip of the container to touch the eye or areas around the eye. To avoid possible contamination, keep the tip of the container away from contact with any surface.

Do not change the dosage of the drug without consulting your doctor. If you must stop treatment, contact your doctor immediately.

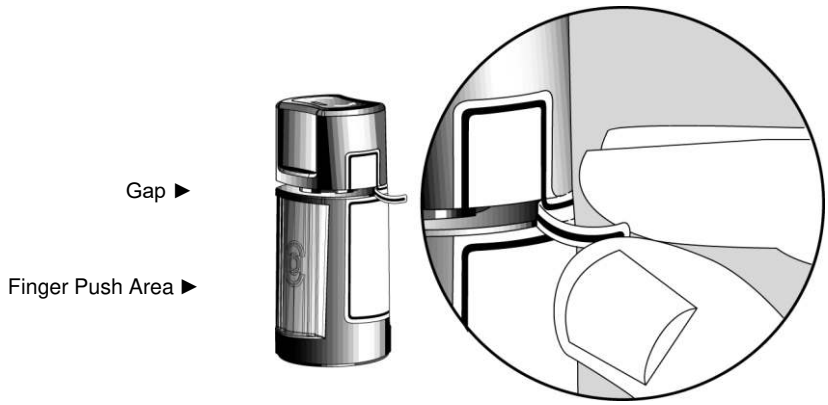
If you have the impression that the effect of TRUSOPT® 2 % is too strong or too weak, talk to your doctor or pharmacist.

Instructions for use

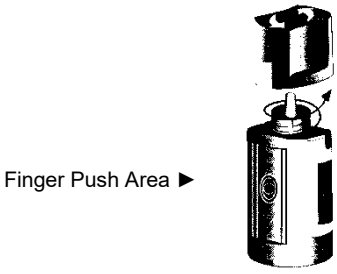
1. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.



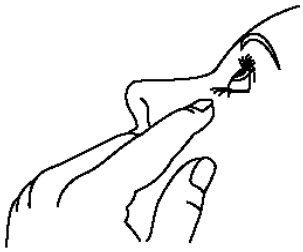
2. Tear off the Safety Strip to break the seal.



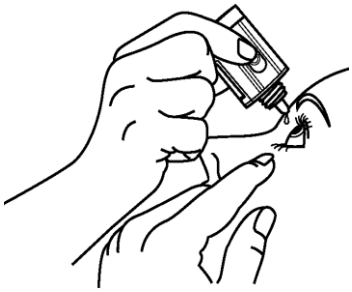
3. To open the bottle, unscrew the cap by turning as indicated by the arrows on the top of the cap. Do not pull the cap back directly up and away from the bottle. Pulling the cap directly up will prevent your dispenser from operating properly.

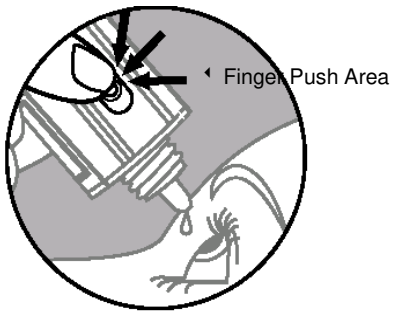


4. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.



5. Invert the bottle and press lightly with the thumb or index finger over the “Finger Push Area” (as shown) until a single drop is dispensed into the eye as directed by your doctor.





DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.
Ophthalmic medications, if handled improperly, can become contaminated by common bacteria known to cause eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications. If you think your medication may be contaminated, or if you develop an eye infection, contact your doctor immediately concerning continued use of this bottle.

6. If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction as indicated by the arrows on top of the cap.
7. Repeat steps 4 and 5 with the other eye if instructed to do so by your doctor.
8. Replace the cap by turning until it is firmly touching the bottle. The arrow on the left side of the cap must be aligned with the arrow on the left side of the bottle label for proper closure. Do not over-tighten or you may damage the bottle and cap.
9. The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.
10. After you have used all doses, there will be some TRUSOPT® 2 % left in the bottle. You should not be concerned since an extra amount of TRUSOPT® 2 % has been added and you will get the full amount of TRUSOPT® 2 % that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

If you use more TRUSOPT® 2 % than you should

If the contents of the bottle are swallowed, you should contact your doctor immediately.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to use TRUSOPT® 2 %

It is important to use TRUSOPT® 2 % as prescribed by your doctor.

If you miss a dose, use it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule.

5. POSSIBLE SIDE EFFECTS

TRUSOPT® can have side effects.

Not all side effects reported for TRUSOPT® are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional.

Although not all these side effects may occur, if they do occur, you may need medical attention.

Patients may experience eye symptoms such as burning and stinging, blurred vision, itching, tearing, redness of the eye(s), eye pain or swelling or crusting of the eyelids.

You may sense a bitter taste after putting in your eye drops.

Other side effects include headache, nose bleed, dry mouth, nausea, tiredness, dizziness, tingling sensation, kidney stones and rarely allergic-type reactions including rash, hives, itching and shortness of breath.

Side effects, other than those listed above, may also occur, and some of these may be serious, such as severe skin reactions. Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

Please tell your doctor/pharmacist promptly about any of these or any other unusual symptoms.

If you noticed any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF TRUSOPT® 2 %

Store all medicines out of reach of children.

Store TRUSOPT® 2 % at or below 25 °C. Protect from light.

Do not use this medicine after the month and year following EXP.: on the container.

DO NOT USE MORE THAN 30 DAYS AFTER OPENING.

Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF TRUSOPT® 2 %

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

8. IDENTIFICATION OF TRUSOPT® 2 %

TRUSOPT® 2 % is a clear, colourless to nearly colourless, slightly viscous solution.

9. REGISTRATION NUMBER

South Africa S3

29/15.4/0766

Namibia NS2

13/15.4/0014

10. NAME AND ADDRESS OF REGISTRATION HOLDER

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