

## 1. Name of the medicinal product

TRUSOPT®

## 2. Qualitative and quantitative composition

Each ml contains 22.26 mg of dorzolamide hydrochloride equivalent to 20 mg of dorzolamide.

Excipient with known effect:

One ml of eye drops solution contains 0.075 mg benzalkonium chloride and one drop contains about 0.002 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Eye drops, ophthalmic solution

Clear, colourless to nearly colourless, slightly viscous, solution.

## 4. Clinical particulars

### 4.1 Therapeutic indications

For the treatment of elevated intraocular pressure in patients with ocular hypertension, open-angle glaucoma and in some patients secondary glaucoma.

### 4.2 Posology and method of administration

#### Posology

The dose is one drop of TRUSOPT Ophthalmic Solution in the affected eye(s) three times daily.

TRUSOPT may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with 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 eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications.

Patients should be informed of the correct handling of the containers.

#### *Pediatric use*

Safety and effectiveness in pediatric patients have not been established.

INSTRUCTIONS FOR USE -see at the end of this SPC.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Dorzolamide has not been studied in patients with severe renal impairment ( $\text{CrCl} < 30 \text{ ml/min}$ ) or with hyperchloraemic acidosis. Because dorzolamide and its metabolites are excreted predominantly by the kidney, dorzolamide is therefore contra-indicated in such patients.

### 4.4 Special warnings and precautions for use

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

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

Dorzolamide contains a sulphonamido group, which also occurs in sulphonamides 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.

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.

If allergic reactions (e.g., conjunctivitis and eye-lid reactions) are observed, discontinuation of treatment should be considered.

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 dorzolamide. The concomitant administration of dorzolamide and oral carbonic anhydrase inhibitors 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. Topical dorzolamide should be used with caution in such patients.

Choroidal detachment concomitant with ocular hypotony have been reported after filtration procedures with administration of aqueous suppressant therapies.

#### Benzalkonium chloride

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.

#### Contact Lens Use

TRUSOPT 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.

#### Pediatric population

Safety and effectiveness in pediatric patients have not been established.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Specific drug interaction studies have not been performed with dorzolamide.

In clinical studies, dorzolamide 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.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Dorzolamide should not be used during pregnancy. There are no or limited amount of data from the use of dorzolamide in pregnant women. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (see section 5.3)

#### Breastfeeding

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 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 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 drug-related ocular adverse reactions, primarily conjunctivitis and lid reactions.

The following adverse reactions have been reported either during clinical trials or during post-marketing experience with dorzolamide:

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

**Nervous system disorders:**

*Common:* headache

*Rare:* dizziness, paraesthesia

**Eye disorders:**

*Very common:* burning and stinging

*Common:* superficial punctate 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

*Not known:* foreign body sensation in eye

**Cardiac disorders:**

*Not known:* palpitations, tachycardia

**Vascular disorders:**

*Not known:* hypertension

**Respiratory, thoracic, and mediastinal disorders:**

*Rare:* epistaxis

*Not known:* dyspnoea

**Gastrointestinal disorders:**

*Common:* nausea, bitter taste

*Rare:* throat irritation, dry mouth

**Skin and subcutaneous tissue disorders:**

*Rare:* contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

**Renal and urinary disorders:**

*Rare:* urolithiasis

**General disorders and administration site conditions:**

*Common:* asthenia/fatigue

*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

**Investigations:**

Dorzolamide was not associated with clinically meaningful electrolyte disturbances.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

## 4.9 Overdose

Only limited information is available with regard to human overdose by accidental or deliberate ingestion of dorzolamide hydrochloride.

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**

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Carbonic Anhydrase Inhibitors, dorzolamide, ATC code: S01EC03

#### Mechanism of Action

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 intra-ocular pressure (IOP).

TRUSOPT contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra-ocular pressure is a major risk factor in the pathogenesis of optic nerve damage and visual-field loss. Dorzolamide does not cause pupillary constriction and reduces intra-ocular pressure without side effects such as night blindness, accommodative spasm. Dorzolamide has minimal or no effect on pulse rate or blood pressure.

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

##### *Adult patients*

In patients with glaucoma or ocular hypertension, the efficacy of dorzolamide given t.i.d. as monotherapy (baseline IOP  $\geq 23$  mmHg) or given b.i.d. as adjunctive therapy while receiving ophthalmic beta-blockers (baseline IOP  $\geq 22$  mmHg) was demonstrated in large-scale clinical studies of up to one-year duration. The IOP-lowering effect of dorzolamide 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, dorzolamide demonstrated additional IOP lowering similar to pilocarpine 2% q.i.d.

### **5.2 Pharmacokinetic properties**

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. 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, active substance and metabolite concentrations in red blood cells (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 active substance in plasma are maintained. 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 non linearly, resulting in a rapid decline of active substance 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 active substance 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. 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.

### **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 a 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 doses of dorzolamide.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Mannitol, Hydroxyethylcellulose, Sodium citrate, Benzalkonium chloride, Sodium hydroxide, Water for injection.

### 6.2 Incompatibilities

Not Applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After first opening the container, TRUSOPT should be used no longer than one month.

### 6.4 Special precautions for storage

Store below 30°C, protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

TRUSOPT container contains 5 ml of solution.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. Marketing authorisation holder

Rafa laboratories Ltd. P.O.Box 405, Jerusalem 9100301

Registration Number: 106-58-28935-00

## 8. Manufacturer:

Fareva Mirabel, Clermont-Ferrand, France

### INSTRUCTIONS FOR USE

#### **Before using your TRUSOPT**

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. (See Figure A).

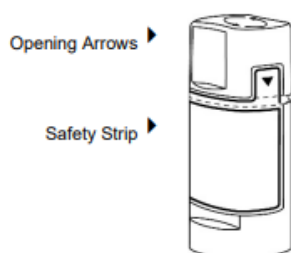


Figure A

**Step 1.** Wash your hands.

**Step 2.** Tear off the safety strip to break the seal. See figure B.

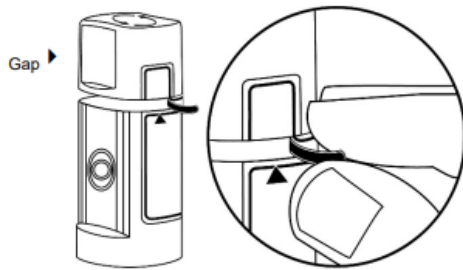


Figure B

**Step 3.** Unscrew the cap by turning in the direction of the arrows on the top of the cap. **Do not** pull the cap directly up and away from the bottle. Pulling the cap directly up will keep your TRUSOPT dispenser from working the right way. See Figure C.

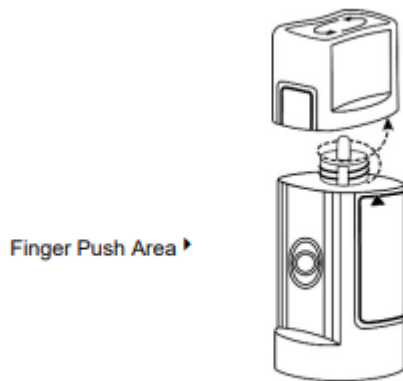


Figure C

#### Giving your TRUSOPT drops

**Step 4.** Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye. See Figure D.

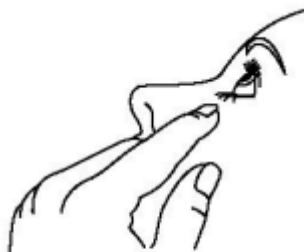


Figure D

**Step 5.** Turn your TRUSOPT dispenser upside down and press lightly with your thumb or index finger over the “Finger Push Area” until a single drop is placed in your eye. **DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.** See Figure E.

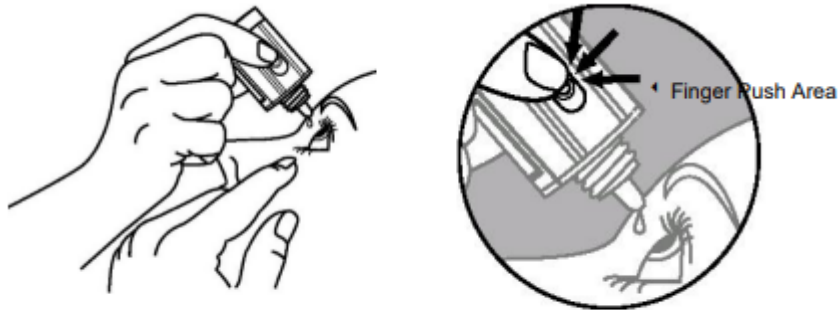


Figure E

**Step 6.** If the medicine does not drop easily from the TRUSOPT dispenser after you open it for the first time, replace the cap on the bottle and tighten. **Do not** over tighten. Remove the cap by turning the cap in the direction of the arrows on the top of the cap. See Figure F. This should make the hole on the dispenser tip larger. **Do not** try to make the hole of the dispenser tip larger in any other way. The dispenser tip is made to provide a single drop. Repeat Steps 4 and 5 to give your TRUSOPT drop.

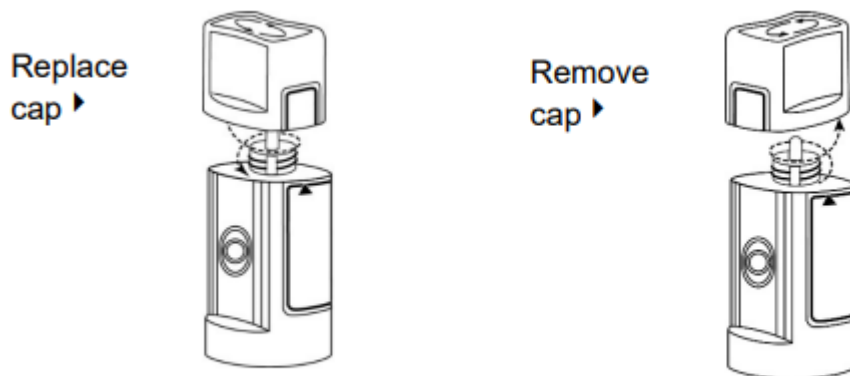


Figure F

**Step 7.** If your doctor has told you to use TRUSOPT drops in both eyes, repeat Steps 4 and 5.

#### After using your TRUSOPT

**Step 8.** Replace the cap by turning until it is firmly touching your TRUSOPT dispenser. **Do not** overtighten or you may damage the TRUSOPT dispenser and cap. See Figure G.

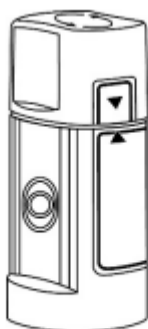


Figure G

After you have used all doses, there will be some TRUSOPT left in the container. You should not be concerned since an extra amount of TRUSOPT has been added and you will get the full amount of TRUSOPT that your doctor prescribed. **Do not** attempt to remove the excess medicine from the container.

Revised in March 2023 according to MOH's guidelines.