

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRUSOPT® 2% Eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20 mg dorzolamide (as 22.3 mg of dorzolamide hydrochloride).

3. PHARMACEUTICAL FORM

Eye drops, solution.

Isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

‘Trusopt’ is indicated:

- ◆ as adjunctive therapy to beta-blockers,
- ◆ as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contra-indicated,

in the treatment of elevated intra-ocular pressure in:

- ◆ ocular hypertension,
- ◆ open-angle glaucoma,
- ◆ pseudo-exfoliative glaucoma.

4.2 Posology and method of administration

When used as monotherapy, the dose is one drop of dorzolamide in the conjunctival sac of the affected eye(s), three times daily.

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

When substituting dorzolamide for another ophthalmic antiglaucoma agent, discontinue the other agent after proper dosing on one day, and start dorzolamide on the next day.

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

Please see section 6.6 ‘Instructions for use and handling.’

Paediatric use:

Safety and effectiveness in children have not been established.

4.3 Contra-indications

Dorzolamide is contra-indicated in patients who are hypersensitive to any component of this product.

Dorzolamide has not been studied in patients with severe renal impairment (CrCl <30 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 special 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 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. If signs of serious reactions of 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.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such 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.

Dorzolamide has not been studied in patients wearing contact lenses. However, 'Trusopt' contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore dorzolamide should not be administered while wearing soft contact lenses. Contact lenses should be removed before application of the drops and not be re-inserted earlier than 15 minutes after use.

4.5 Interactions with other medicinal products and other forms of interactions

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.

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

4.6 Pregnancy and lactation

Pregnancy: No studies were performed on pregnant women. Dorzolamide should not be used during pregnancy. In rabbits given maternotoxic doses associated with metabolic acidosis, malformations of the vertebral bodies were observed.

Lactation: There are no data showing whether the drug is excreted in human milk. Dorzolamide should not be used during lactation. In lactating rats, decreases in the body-weight gain of offspring were observed.

4.7 Effects on ability to drive and use machines

Possible side effects such as dizziness and visual disturbances may affect the ability to drive and use machines (see also 4.8 'Undesirable effects').

4.8 Undesirable effects

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

Eye disorders: burning and stinging, blurred vision, eye itching, tearing, conjunctivitis, eyelid inflammation, eyelid irritation, eyelid crusting, irritation including redness, pain, superficial punctate keratitis, corneal oedema, iridocyclitis, transient myopia (which resolved upon discontinuation of therapy), ocular hypotony and choroidal detachment following filtration surgery (see also 4.4);

General disorders: Hypersensitivity: signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm;

Gastro-intestinal disorders: bitter taste, nausea, dry mouth, throat irritation;

Respiratory disorders: epistaxis;

Skin disorders: contact dermatitis;

Nervous system disorders: headache, asthenia/fatigue, dizziness, paraesthesia;

Renal and urinary disorders: urolithiasis;

Laboratory findings: Dorzolamide was not associated with clinically meaningful electrolyte disturbances.

4.9 Overdose

Only limited information is available with regard to human overdosage by accidental or deliberate ingestion of dorzolamide hydrochloride. The following have been reported with oral ingestion: somnolence; topical application: nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia.

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

ATC code: S01 EC 03

Topical anti-glaucomatous agent.

Carbonic anhydrase inhibitor.

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-humor 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 humor 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.

Pharmacodynamic effects

Clinical effects: In patients with glaucoma or ocular hypertension, the efficacy of dorzolamide given t.d.s. as monotherapy (baseline IOP ≥ 23 mmHg) or given b.d. as adjunctive therapy while receiving ophthalmic beta-blockers (baseline IOP ≥ 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.d.s.

5.2 Pharmacokinetic properties

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the drug 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, drug and metabolite concentrations in 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 drug in plasma are maintained. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug 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 drug 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 drug 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 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

Hydroxyethyl cellulose, mannitol, sodium citrate, sodium hydroxide (to adjust q.s. pH = 5.65), benzalkonium chloride, water for injections.

6.2 Incompatibilities

None known.

6.3 Shelf-life

The shelf-life is 2 years.

‘Trusopt’ should be used no longer than 28 days after first opening of the container.

6.4 Special precautions for storage

Store bottle in outer carton.

6.5 Nature and contents of container

The OCUMETER Plus ophthalmic dispenser consists of a translucent, high-density polyethylene container with a sealed dropper tip, a flexible fluted side area which is depressed to dispense the drops, and a two-piece cap assembly. The two-piece cap mechanism punctures the sealed dropper tip upon initial use, then locks together to provide a single cap during the usage period. Tamper evidence is provided by a safety strip on the container label. The OCUMETER Plus ophthalmic dispenser contains 5 ml of solution.

‘Trusopt’ is available in the following packaging configurations:

1 x 5 ml (single 5-ml container)

3 x 5 ml (three 5-ml containers)

6 x 5 ml (six 5-ml containers)

6.6 Instructions for use and handling

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 infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should be informed of the correct handling of the OCUMETER Plus bottles.

Usage instructions:

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.
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" 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.**
6. Repeat steps 4 & 5 with the other eye if instructed to do so by your doctor.
7. Replace the cap by turning until it is firmly touching the bottle. Do not over-tighten the cap.
8. The dispenser tip is designed to provide a pre-measured drop; therefore, do NOT enlarge the hole of the dispenser tip.
9. After you have used all doses, there will be some 'Trusopt' left in the bottle. 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 bottle.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road,
Hoddesdon,
Hertfordshire EN11 9BU,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

MA058/00401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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LEGAL CATEGORY

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