AUSTRALIAN PRODUCT INFORMATION

TRUSAMIDE

(dorzolamide hydrochloride) eye drops

1 NAME OF THE MEDICINE

Dorzolamide hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: benzalkonium chloride.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, slightly viscous, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRUSAMIDE eye drops are indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

4.2 DOSE AND METHOD OF ADMINISTRATION

For individual patient use only.

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

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

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

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

Systemic absorption of drugs from ophthalmic solutions may be minimised by pressure on the tear-duct immediately after application.

4.3 CONTRAINDICATIONS

TRUSAMIDE is contraindicated in patients with severe renal impairment and who are hypersensitive to any component of this product.

Dorzolamide hydrochloride eye drops has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or with hyperchloremic acidosis. Because dorzolamide hydrochloride eye drops and its metabolites are excreted predominantly by the kidney, dorzolamide hydrochloride eye drops is therefore contraindicated in such patients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

Dorzolamide hydrochloride eye drops 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. The safety of dorzolamide hydrochloride eye drops has not been demonstrated in patients with known hypersensitivity to sulphonamides. 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.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide hydrochloride eye drops. 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 with dorzolamide hydrochloride eye drops 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 hydrochloride eye drops. The concomitant administration of dorzolamide hydrochloride eye drops 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 dorzolamide. Topical dorzolamide should be used with caution in such patients. Choroidal detachment concomitant with ocular hypotony has been reported with administration of dorzolamide after filtration procedures.

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

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 wash their hands before use and 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 also be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), or any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice concerning the continued use of the product.

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

Excipient with Known Effect

TRUSAMIDE contains 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

TRUSAMIDE contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses and may change the colour of contact lenses. Therefore, TRUSAMIDE 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.

Use in Hepatic Impairment

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

Use in Renal Impairment

Dorzolamide is contraindicated in patients with severe renal impairment. Refer to information in Section 4.3 CONTRAINDICATIONS.

Use in the Elderly

Of the total number of patients in clinical studies of dorzolamide hydrochloride eye drops, 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.

Paediatric Use

Safety and effectiveness in children have not been established as there have been no trials in children.

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. From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Effects on Laboratory Tests

Dorzolamide hydrochloride eye drops was not associated with clinically meaningful electrolyte disturbances.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific drug interaction studies have not been performed with dorzolamide hydrochloride eye drops. In clinical studies, dorzolamide hydrochloride eye drops 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. estrogen, insulin, thyroxine).

Dorzolamide hydrochloride eye drops is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. Dorzolamide hydrochloride eye drops should not be used concomitantly with oral carbonic anhydrase inhibitors.

In clinical studies, dorzolamide hydrochloride eye drops 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 hydrochloride eye drops.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

In reproduction studies of dorzolamide hydrochloride in rats, there were no adverse effects on the reproductive capacity of males or females at oral doses up to 15 and 7.5 mg/kg/day, respectively.

Use in Pregnancy (Category B3)

There are no adequate and well controlled studies in pregnant women. Dorzolamide hydrochloride eye drops should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (fetal red blood cell C_{max} was approximately twice the maternal red blood cell C_{max} after the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related malformations were seen at 1 mg/kg/day. There were no treatment related fetal malformations in developmental toxicity studies with dorzolamide hydrochloride in rats at oral doses up to 10 mg/kg/day.

Use in Lactation

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain in offspring were seen during lactation after an oral dose of 7.5 mg/kg/day. A slight delay in postnatal development (incisor eruption, vaginal canalisation and eye opening), secondary to lower fetal body weight, was noted.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are potential side effects of dorzolamide hydrochloride eye drops that may affect some patients' ability to drive and use machines (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Dorzolamide hydrochloride eye drops were evaluated in more than 1400 individuals in controlled and uncontrolled clinical studies. In long term studies of 1108 patients treated with dorzolamide hydrochloride eye drops as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with dorzolamide hydrochloride eye drops was drug-related ocular adverse effects consistent with allergic-type reactions, primarily conjunctivitis and lid reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Such reactions occurred approximately 7% overall in the clinical trials.

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

Adverse experiences reported during clinical studies as drug-related (possibly, probably, or definitely) in 1-5% of patients on dorzolamide hydrochloride eye drops 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:

Cardiac disorders:	Tachycardia
Hypersensitivity:	Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm
Nervous System:	Dizziness, paraesthesia
Ocular:	Pain, redness, transient myopia (which resolved upon discontinuation of therapy), corneal oedema, ocular hypotony, superficial punctate keratitis, eyelid crusting, choroidal detachment following filtration surgery, foreign body sensation
Skin/Mucous Membranes:	Contact dermatitis, epistaxis, throat irritation, dry mouth, Stevens-Johnson syndrome, toxic epidermal necrolysis
Respiratory:	Dyspnoea
Urogenital:	Urolithiasis
Vascular disorders:	Hypertension

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Somnolence has been reported with overdoses via oral ingestion of dorzolamide. Nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia have been reported with topical application.

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.

Significant lethality was observed in female rats and mice after single oral doses of dorzolamide hydrochloride of 11,369 mg/m^2 (1927 mg/kg) and 3960 mg/m^2 (1320 mg/kg), respectively.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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.

Mechanism of Action

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 humor 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).

TRUSAMIDE eye drops contain dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide hydrochloride eye drops 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. Dorzolamide hydrochloride eye drops does not cause pupillary constriction and reduces intraocular pressure without the side effects such as night blindness and accommodative spasm. Dorzolamide hydrochloride eye drops 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 hydrochloride eye drops 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 Trials

In clinical studies for up to one year in patients with glaucoma or ocular hypertension (baseline IOP $\geq$ 23 mm Hg), the IOP-lowering effect of dorzolamide hydrochloride eye drops was approximately 3 to 5 mm Hg throughout the day. However, as with other IOP lowering drugs, diminished responsiveness after prolonged therapy has been observed in some patients.

5.2 PHARMACOKINETIC PROPERTIES

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 nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the maximum systemic exposure after long term topical ocular administration, dorzolamide hydrochloride eye drops was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 4 mg/day closely approximates the maximum amount of drug delivered by topical ocular administration of dorzolamide hydrochloride eye drops 2% t.i.d. Steady state was reached within 13 weeks, and the following observations were noted:

- in plasma, concentrations of dorzolamide and metabolite were generally below the assay limit of quantitation (15 nM) indicating almost no free drug or metabolite;

- in RBCs, dorzolamide concentrations approached the binding capacity of CA-II (20-25 μM) and metabolite concentrations approached 12-15 μM, well below the binding capacity of CA-I (125-155 μM);

- in RBCs, CA-II activity was inhibited 94-96% and total carbonic anhydrase activity was inhibited 81-88%. This was below the > 99% inhibition of CA-II activity and 96% inhibition of total carbonic

anhydrase activity in RBCs that are anticipated to be necessary for a pharmacological effect on renal function and respiration, respectively.

In a subset of 71 patients in a large clinical study (N=333) of dorzolamide hydrochloride eye drops t.i.d. in patients with elevated IOP, dorzolamide and metabolite concentrations and carbonic anhydrase inhibition in RBCs were measured after approximately six and twelve months of treatment. The pharmacokinetic results were consistent with those observed at steady state in the oral pharmacokinetic study in terms of CA-II inhibition. Although in this study several patients 65 years of age and older with renal impairment (estimated CrCl 30-60 mL/min) had higher metabolite concentrations in RBCs, 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

Genotoxicity

Dorzolamide showed no mutagenic potential in a series of standard assays for gene mutations, chromosomal damage and DNA damage.

Carcinogenicity

In a 2 year study of dorzolamide administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day. No treatment-related tumours were seen in a 21 month study in male and female mice given oral doses up to 75 and 37.5 mg/kg/day, respectively.

The increased incidence of urinary bladder papillomas seen in the high dose male rats appears to be a class effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for 1 year at doses of 2 mg/kg/day or in monkeys given 20 μL of 3% dorzolamide hydrochloride topically to the eye b.i.d for 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TRUSAMIDE contains the following inactive ingredients: sodium citrate dihydrate, hyetellose, sodium hydroxide, mannitol and water for injections. Benzalkonium chloride (0.0075%) is added as preservative.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store TRUSAMIDE eye drops below 30°C. Protect from light. To be used within 4 weeks after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

TRUSAMIDE eye drops is available in a polyethylene dispensing bottle. Each bottle contains 5 mL of solution and is supplied in 1 x 5 mL bottle packs.

Australian Register of Therapeutic Goods (ARTG)

AUST R 217251– TRUSAMIDE dorzolamide (as hydrochloride) 20 mg/mL eye drops bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Dorzolamide hydrochloride is optically active.

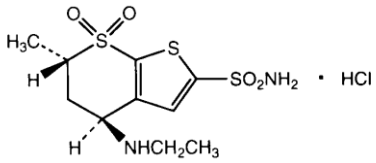
The specific rotation is: $\alpha^{25°}_{405}$ (C=1, water) = ~ -17°.

Dorzolamide hydrochloride has a molecular weight of 360.9 and a melting point of about 275°C. It is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Chemical Structure

Dorzolamide hydrochloride is described chemically as: (4*S*, 6*S*)-4-ethylamino-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride.

Its empirical formula is $C_{10}H_{17}N_2O_4S_3Cl$ and its structural formula is:



CAS Number

130693-82-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

25/09/2014

10 DATE OF REVISION

12/09/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.3	Move to text regarding severe renal impairment (CrCl < 30 mL/min) from under 'Use in Renal Impairment' heading in Section 4.4 to Section 4.3. Inclusion of hyperchloremic acidosis. Change use from ‘not recommended’ to ‘contraindicated’.
4.4	Removal of existing guidance regarding use in patients with severe renal impairment (relocation to contraindications).
4.8	In the adverse reactions reported in post-marketing experience, addition of tachycardia, rash, shortness of breath, rarely bronchospasm, and hypertension.

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