Bar prints 100mm @ 100%

Santen | COMMERCIAL ARTWORK

Description:	Trusopt 2% (MY) 5 ml Leaflet
CMO Item Number:	N/A
CMO SPEC Number:	N/A
GLAMS Part Number:	CAW-5804-01
Technical Drawing No:	N/A
Dimension:	387 X 240 mm
Pharma Code:	7842
2D matrix:	N/A
Date:	14-03-2023
Market:	MY
Material Code:	754776
Artwork Version Number:	03
Schawk Job No.:	108421419/403221570

Printable Colours:

Santen PI Blue

Non Print:

Profile Technical Info

SGK

SGK is a Matthews International Corporation

7842

75477603

LOCAL PRODUCT CIRCULAR
Sterile Ophthalmic Solution

TRUSOPT®

(dorzolamide hydrochloride ophthalmic solution)

Santen

I. THERAPEUTIC CLASS

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

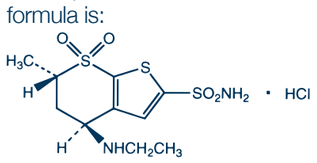
II. CHEMISTRY

TRUSOPT Sterile Ophthalmic Solution contains dorzolamide hydrochloride, which is described chemically as: (4*S-trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*] thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride.

Dorzolamide hydrochloride is optically active.

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

Its empirical formula is $C_{10}H_{16}N_2O_4S_3$. HCl and its structural formula is:



Dorzolamide hydrochloride has a molecular weight of 360.9 and a melting point of about 264°C. It is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

III. COMPOSITION

Active Ingredient (all formulations):

TRUSOPT Sterile Ophthalmic Solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride. Each mL of TRUSOPT 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride).

Inactive ingredients:

TRUSOPT Ophthalmic Solution: hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

IV. CLINICAL PHARMACOLOGY

IVa. Mechanism of Action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes 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).

TRUSOPT Ophthalmic Solution contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, TRUSOPT reduces elevated IOP, whether or not associated with glaucoma. Elevated IOP is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Unlike miotics, TRUSOPT reduces IOP without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Unlike topical beta-blockers, TRUSOPT 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 TRUSOPT 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.

IVb. Pharmacokinetics/Pharmacodynamics

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 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 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 TRUSOPT 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 (15nM) 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 TRUSOPT 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.

V. INDICATIONS

TRUSOPT Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure (IOP) in patients with:

- ocular hypertension
- open-angle glaucoma

VI. DOSAGE AND ADMINISTRATION

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

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

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

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

VII. CONTRAINDICATIONS

TRUSOPT is contraindicated in patients who are hypersensitive to any component of this product.

VIII. PRECAUTIONS

TRUSOPT has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because TRUSOPT and its metabolite are excreted predominantly by the kidney, TRUSOPT is not recommended in such patients.

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

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

TRUSOPT is a sulfonamide and although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of TRUSOPT. 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 TRUSOPT 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 TRUSOPT. The concomitant administration of TRUSOPT and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., dorzolamide) after filtration procedures.

TRUSOPT Ophthalmic Solution contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore, TRUSOPT 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.

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

MUTAGENESIS, CARCINOGENESIS AND IMPAIRMENT OF FERTILITY

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

The increased incidence of urinary bladder papillomas seen in the high-dose male rats appears to be 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 2mg/kg/day or in monkeys given 20µL of 3% dorzolamide hydrochloride topically to the eye bid of 1 year.

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

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 7.5mg/kg/day.

IX. USE IN PREGNANCY

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

X. NURSING MOTHER

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.

XI. PEDIATRIC USE

Safety and effectiveness in children have not been established.

XII. USE IN ELDERLY

Of the total number of patients in clinical studies of TRUSOPT, 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.

XIII. DRUG INTERACTIONS

Specific drug interaction studies have not been performed with TRUSOPT Ophthalmic Solution. In clinical studies, TRUSOPT 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).

TRUSOPT is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, TRUSOPT 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 TRUSOPT.

XIV. SIDE EFFECT

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:

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

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.

XV. LABORATORY FINDINGS

TRUSOPT was not associated with clinically meaningful electrolyte disturbances.

XVI. OVERDOSAGE

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.

XVII. AVAILABILITY

TRUSOPT Ophthalmic Solution is available in packs of 5mL x 1's.
TRUSOPT Ophthalmic Solution is a clear, colorless to nearly colorless, slightly viscous solution.

XVIII. STORAGE

Store below 30°C. Protect from light.
Discard one month after opening container.

SHELF LIFE

36 months

XIX. MANUFACTURED & PACKED BY:

SANTEN PHARMACEUTICAL CO., LTD.
Noto plant: Ishikawa, Japan

XX. PRODUCT REGISTRATION HOLDER

SANTEN PHARMA MALAYSIA SDN. BHD.
(1117719-T)
Unit #23A-10, Q Sentral,
No. 2A, Jalan Stesen Sentral 2, Kuala Lumpur Sentral,
50470 Kuala Lumpur, Malaysia.

DATE OF REVISION: Jan 2021

03

Approved 26-Mar-2023 23-03 UTC

Username	Full Name	Status	Date/Time (UTC)
GaithriGanesan	Gaithri Ganesan	Approved	21-Mar-2023 00-57 UTC
ShirleyTok	Shirley Tok	Approved	21-Mar-2023 01-14 UTC
KahPeiLau	Kah Pei Lau	Approved	21-Mar-2023 02-51 UTC
CalvinLow	Calvin Low	Approved	21-Mar-2023 06-33 UTC
GraceLou	Grace Lou	Approved	25-Mar-2023 00-44 UTC
KazuhiroNishino	Kazuhiro Nishino	Approved	26-Mar-2023 23-03 UTC