Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DORZOLAMIDE ADCO, 20 mg, eye drops solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains dorzolamide hydrochloride equivalent to 20 mg dorzolamide.

Preservative free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops solution.
Clear, slightly viscous, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DORZOLAMIDE ADCO is indicated in the treatment of elevated intraocular pressure (IOP) in patients with:

- ocular hypertension;
- open-angle glaucoma;
- pseudoexfoliative glaucoma or other secondary open-angle glaucomas; and
- short term treatment of paediatric glaucomas as adjunctive therapy to beta-blockers and for monotherapy.

4.2 Posology and method of administration

Posology

- When used as monotherapy, the dose is one drop of DORZOLAMIDE ADCO in the affected eye(s) 3 times daily.
- When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of DORZOLAMIDE ADCO in the affected eye(s) 2 times per day.

When substituting DORZOLAMIDE ADCO for another ophthalmic anti-glaucoma medicine, discontinue the other medicine after proper dosing in one day, and start DORZOLAMIDE ADCO on the next day. If more than one topical ophthalmic medicine is being used, the medicines should be administered at least 10 minutes apart.

Special populations

Paediatric population

Currently available data are described in section 5.1.

Method of administration
For topical ophthalmic use

4.3 Contraindications

- DORZOLAMIDE ADCO is contraindicated in patients with hypersensitivity to dorzolamide or any of the excipients listed in section 6.1.
- Dorzolamide has not been studied in patients with moderate progressing to severe renal impairment (CrCl < 30 mL/min) or with hyperchloraemic acidosis. Dorzolamide and its metabolites are excreted predominantly by the kidney. DORZOLAMIDE ADCO is therefore contra-indicated in such patients.

4.4 Special warnings and precautions for use
DORZOLAMIDE ADCO 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 ADCO has not been studied in patients with acute angle-closure glaucoma.

DORZOLAMIDE ADCO contains a sulphonamide 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 DORZOLAMIDE ADCO, including severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, 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 DORZOLAMIDE ADCO.

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. DORZOLAMIDE ADCO is a topical carbonic anhydrase inhibitor that is absorbed systemically, therefore patients with a prior history of renal calculi may be at increased risk of urolithiasis. 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.

Local ocular adverse effects, primarily conjunctivitis and lid reactions, have been reported with chronic administration of DORZOLAMIDE ADCO. 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 DORZOLAMIDE ADCO should be discontinued and the patient evaluated before considering restarting the medicine.

There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. In addition, 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 topical dorzolamide. DORZOLAMIDE ADCO 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.

Use in the Elderly
In clinical studies conducted with dorzolamide as in DORZOLAMIDE ADCO, no overall differences in effectiveness or safety were observed in patients 65 years of age and older. However, greater sensitivity of some older individuals cannot be ruled out.

Paediatric Population
Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. 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.

4.5 Interactions with other medicines and other forms of interaction
Specific interaction studies have not been performed with DORZOLAMIDE ADCO.
In clinical studies where an ophthalmic solution containing dorzolamide hydrochloride were used concomitantly with the following medicines, no adverse interactions were reported: Timolol ophthalmic solution, betaxolol ophthalmic solution and systemic medicines, including ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines (e.g. aspirin), and hormones (e.g. Oestrogen, insulin, thyroxine).

Association between DORZOLAMIDE ADCO and miotics and adrenergic agonists have not been fully evaluated during glaucoma therapy.

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

4.6 Fertility, pregnancy and lactation
Fertility
Animal data do not suggest an effect of treatment with dorzolamide on male and female fertility. Human data are lacking.

Pregnancy

There are not adequate and well-controlled studies in pregnant women. Therefore, DORZOLAMIDE ADCO should not be used during pregnancy. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses.

Breastfeeding

It is not known whether dorzolamide or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dorzolamide/metabolites in milk.

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

The following adverse reactions have been reported with dorzolamide hydrochloride ophthalmic solution (as DORZOLAMIDE ADCO):

Tabulated summary of adverse reactions
Dorzolamide hydrochloride

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Nervous system disorders	Headache	Dizziness, paraesthesia	-
Eye disorders	Burning and stinging eyes, superficial punctuate keratitis, tearing, conjunctivitis, eyelid inflammation, eye itching, eyelid irritation, blurred vision	Iridocyclitis, irritation including redness, pain, eyelid crusting, transient myopia (which resolves upon discontinuation of therapy), corneal oedema, ocular hypotony, choroidal detachment (following filtration surgery)	Foreign body sensation in eye
Cardiac disorders	-	-	Palpitations
Respiratory, thoracic, and mediastinal disorders	-	Epistaxis	Dyspnoea
Gastrointestinal disorders	Nausea, bitter taste	Throat irritation, dry mouth	-
Skin and subcutaneous tissue disorders	-	Contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	-
Renal and urinary disorders	-	Urolithiasis	-
General disorders and administration site conditions	Asthenia/fatigue	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 ADCO was not associated with clinically meaningful electrolyte disturbances.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological classification: A.15.4 Ophthalmic preparations, other.
Anatomical Therapeutic Chemical Classification (ATC Code): S01 EC03

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).

DORZOLAMIDE ADCO contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular pressure, whether associated with glaucoma or not. 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.

Paediatric population
Safety and IOP-lowering effects of dorzolamide have been evaluated in paediatric patients younger than 6 years of age with glaucoma or elevated intraocular pressure (baseline IOP higher than 22 mmHg). Use of dorzolamide in this age group is supported by evidence from a 3-month controlled study.

5.2 Pharmacokinetic properties
Unlike oral carbonic anhydrase inhibitors, topical administration allows dorzolamide hydrochloride 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, medicine 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 low concentrations of free medicine in plasma are maintained. The parent medicine forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent medicine 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 medicine 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 hydrochloride. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxy ethyl cellulose
Mannitol,
Sodium citrate dihydrate
Sodium hydroxide
Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
DORZOLAMIDE ADCO should be used no longer than 28 days after first opening the container.

6.4 Special precautions for storage

Store at or below 25 °C.
DORZOLAMIDE ADCO should not be used more than 28 days after opening.

6.5 Nature and contents of container

DORZOLAMIDE ADCO eye drops solution is packed in a 11 mL white opaque LDPE bottle with a white HDPE Novelia nozzle/cap subassembly (containing a silicone valve, spring and plug), closed with a white HDPE screw cap and packed in an outer carton. Each bottle contains 5 mL in a 11 mL bottle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK (232652)

8. REGISTRATION NUMBER(S)

56/15.4/0842.841

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 October 2024

10. DATE OF REVISION OF THE TEXT