SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

OCUDOR (Dorzolamide Eye Drops BP 2% w/v)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Dorzolamide Hydrochloride ……..... 22.3 mg
Equivalent to Dorzolamide …… 20.0 mg
Benzalkonium Chloride …… 0.075 mg
(As Preservative)
Aqueous buffered Vehicle…….. q.s.

3. PHARMACEUTICAL FORM

Ophthalmic Solution

Description

A clear, colourless slightly viscous solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OCUDOR Eye Drops are indicated:
1. As an adjunctive therapy to beta-blockers.
2. As a monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated.
3. In the treatment of elevated intra-ocular pressure (IOP) in ocular hypertension, open angle glaucoma, and pseudoexfoliative glaucoma.

4.2 Posology and method of administration

For occular administration in adults and children

1. When used as monotherapy, the dose is one drop of dorzolamide in the conjunctival sac of the affected eye(s), three times daily.
2. 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.
3. When substituting dorzolamide for another ophthalmic anti-glaucoma 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 10 minutes apart.
The dosage and duration of the treatment should be as recommended by the doctor.
If one dose is missed, treatment should continue with the next dose as normal.

Paediatric Population

Limited clinical data in paediatric patients with administration of dorzolamide three times a day are available (for further information, refer section 4.4).

Method of Administration

1. First wash your hands.
2. Avoid touching the eye (or any other surface) with the tip of the bottle so as to avoid microbial contamination of the solution.

3. If you wear soft contact lenses, they should be removed before using the eye drops and wait at least 15 minutesbefore reinserting.
4. These drops are supplied in a plastic bottle with an insert cap assembly, with a tamper proof dust cover. When usingthe bottle for the first time, snap off the dust cover by turning it clockwise to break the seal.
5. Unscrew the inner cap.
6. Tilt your head back and look at the ceiling.
7. Pull the lower eyelid gently downwards to form a pocket between your eyelid and your eye.
8. Hold the bottle upside down above the eye and gently squeeze the bottle to release a drop into your eye. Do not touch your eye or eyelid with the dropper tip.
9. Keep the affected eye closed and press your fingertip against the inside corner of the closed eye, and hold for 2 minute. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.
10. Repeat for the other eye if instructed to do so by your doctor.
11. Recap the bottle after every use, tighten the inner cap on the nozzle.

4.3 Contraindications

Hypersensitivity to dorzolamide or to any of the excipients listed in section 6.1.
Dorzolamide has not been studied in patients with severe renal impairment (CrCl < 30 ml/min) or with hyperchloraemicacidosis. Because dorzolamide and its metabolites are excreted predominantly by the kidney, dorzolamide is therefore contraindicated 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 (SJS) and toxic epidermal necrolysis (TEN). 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 carbonicanhydrase 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 chroniccorneal defects and/or a history of intra-ocular surgery while using dorzolamide ophthalmic solution. 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.

This product contains the preservative benzalkonium chloride. Use of benzalkoniumchloride with soft contact lenses should be avoided. Contact lenses should be removed prior to application and wait atleast 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film andcorneal 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.

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 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 (NSAIDs) 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 dorzolamidein pregnant women. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses.

Breast Feeding
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 dorzolamide therapy taking into account the benefit of breastfeeding 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
Dorzolamide Ophthalmic Solution was evaluated in more than 1400 individuals in controlled and uncontrolled clinical studies. In long-term studies of 1108 patients treated with dorzolamide as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with Dorzolamide Eye Drops was drug-related ocular adversereactions, primarily conjunctivitis and lid reactions.

The following adverse reactions have been reported either during clinical trials or during post-marketing experience withdorzolamide:
[Very common: (≥ 1/10), Common: (≥ 1/100 to <1/10), Uncommon: (≥ 1/1,000 to <1/100), Rare: (≥ 1/10,000 to <1/1,000), Not known: (cannot be estimated from the available data)].

Organ System	Very Common	Common	Uncommon	Rare	Not known
Nervous system disorders		headache.		dizziness, paraesthesia.	
Cardiac disorders					palpitations, tachycardia.
Eye disorders	burning and stinging	superficial punctate keratitis, tearing, conjunctivitis, eyelid inflammation,eye itching, eyelid irritation, blurred vision.	iridocyclitis.	irritation including redness, pain, eyelid crusting, transient myopia (which resolved upon discontinuation of therapy), corneal oedema, ocular hypotony, choroidal detachment following filtration surgery.	foreign body sensation in eye
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.		hypersensitivity: signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactionsincluding angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm.	
Vascular disorders					hypertension.

Reporting of 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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4.9 Overdose

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

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, carbonicanhydrase 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). Dorzolamide is a potent inhibitor of human carbonicanhydrase II.

Pharmacodynamic Effects

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

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 ≥23 mmHg) or given b.i.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 similarto pilocarpine 2% q.i.d.

Paediatric Population

A 3-month, double-masked, active-treatment controlled, multicentre study was undertaken in 184 (122 for dorzolamide) paediatric patients from 1 week of age to <6 years of age with glaucoma or elevated intraocular pressure (baseline IOP ≥22 mmHg) to assess the safety of Dorzolamide Eye Drops 2% w/v when administered topically t.i.d. Approximately half the patients in both treatment groups were diagnosed with congenital glaucoma; other common aetiologies were Sturge Weber syndrome, iridocorneal mesenchymal dysgenesis, aphakic patients.

The distribution by age and treatments in the monotherapy phase was as follows:

	Dorzolamide 2%	Timolol
Age cohort < 2 years	N=56 Age range: 1 to 23 months	Timolol GS 0.25% N=27 Age range: 0.25 to 22 months
Age cohort ≥ 2 to < 6 years	N=66 Age range: 2 to 6 years	Timolol 0.50% N=35 Age range: 2 to 6 years

Across both age cohorts approximately 70 patients received treatment for at least 61 days and approximately 50 patientsreceived 81-100 days of treatment.

If IOP was inadequately controlled on dorzolamide or timolol gel-forming solution monotherapy, a change was made to open-label therapy according to the following: 30 patients <2 years were switched

to concomitant therapy with timolol gel-forming solution 0.25% daily and dorzolamide 2% t.i.d.; 30 patients ≥2 years were switched to 2% dorzolamide/0.5% timolol fixed combination b.i.d.
Overall, this study did not reveal additional safety concerns in paediatric patients: approximately 26% (20% in dorzolamide monotherapy) of paediatric patients were observed to experience drug related adverse affects, the majority of which were local, non-serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage <4% was observed to have corneal oedema or haze. Local reactions appeared similar in frequency to comparator. In post-marketing data, metabolic acidosis in the very young particularly with renal immaturity/impairmenthas been reported.
Efficacy results in paediatric patients suggest that the mean IOP decrease observed in the dorzolamide group was comparable to the mean IOP decrease observed in the timolol group even if a slight numeric advantage was observed for timolol.
Longer-term efficacy studies (>12 weeks) are not available.

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 effecton 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 PARTICULAR

6.1 List of excipients

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

6.2 Incompatibilities

Not known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at a temperature not exceeding 25^0C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container

5ml solution filled in 5ml labelled insert bottle packed in a carton with pack insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Registered Office:
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8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 07174/08322/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar 4, 2022

10. DATE OF REVISION OF THE TEXT

September 2023.