1. NAME OF THE MEDICINAL PRODUCT

Dorzostill 20 mg/ml, oogdruppels, oplossing

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20.0 mg dorzolamide (as 22.3 mg dorzolamide hydrochloride).
Excipient(s) with known effect:
contains benzalkonium chloride 0.075 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear or slightly opalescent, colourless, particle free, isotonic, buffered slightly viscous aqueous solution with pH approx. 5.65.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Nationally completed name> is indicated:

- as adjunctive therapy to beta-blockers,
- as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated,

in the treatment of elevated intra-ocular pressure in:

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

4.2 Posology and method of administration

Route of administration: for ocular use.

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 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 medicinal product is being used, the products should be administered at least ten minutes apart.

See section 4.4 concerning the use of contact lenses.

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.

Method of administration:

1. To open the bottle unscrew the cap.

2. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.

3. Invert the bottle, and press lightly until a single drop is dispensed into the eye as directed by your doctor. Do not touch your eye or eye lid with the dropper tip. 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

4. Repeat steps 2 & 3 with the other eye if instructed to do so by your doctor.

Replace the cap immediately after use by screwing down until it is firmly touching the bottle. Do not over-tighten the cap.

The dispenser tip is designed to provide a pre-measured drop; therefore, do not enlarge the hole of the dispenser tip. After you have used all doses, there will be some <Nationally completed name> left in the bottle. You should not be concerned since an extra amount of <Nationally completed name> has been added and you will get the full amount of <Nationally completed name> that your doctor prescribed. Do not attempt to remove the excess medicine from the bottle.

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Paediatric population:
Limited clinical data in paediatric patients with administration of dorzolamide three times a day are available. (For information regarding paediatric dosing see section 5.1).

4.3 Contraindications
Hypersensitive to the active substance 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 hyperchloraemic acidosis. 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 sulphonamide group, which also occurs in sulfonamides 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. 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.

If allergic reactions (eg. conjunctivitis and eyelid 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 eye drops containing dorzolamide. 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.

<Nationally completed name> contains 0.0022 mg benzalkonium chloride in each drop which is equivalent to 0.075 mg/ml
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 lenses should be removed prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

Paediatric population:
Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than one 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 agents 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, no acid-base disturbances have been observed with dorzolamide. These reactions were

observed after use of oral carbonic anhydrase inhibitors and resulted in some cases in interaction with other medicinal products (e.g. toxic reactions in patients undergoing therapy with high doses of salicylates). Therefore, possibility of such interactions should be considered for patients receiving dorzolamide.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Dorzolamide should not be used during pregnancy. No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (see Section 5.3).

Breastfeeding:

It is not known whether dorzolamide is excreted in human milk. In lactating rats, decreases in the body weight gain of offspring were observed. If treatment with dorzolamide is required, then lactation is not recommended.

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 (see also section 4.8).

4.8 Undesirable effects

Eye drops containing dorzolamide were evaluated in more than 1400 individuals in controlled and uncontrolled clinical studies. In long term studies of 1108 patients treated with eye drops containing dorzolamide as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with eye drops containing dorzolamide was product related ocular adverse effects, primarily conjunctivitis and lid reactions.

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

	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***
Immune system 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	
Nervous system disorders:		• headache		• dizziness, • paraesthesia	

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
Cardiac disorders					• Palpitations • *Tachycardia*
Vascular disorders					• *Hypertension*
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		•	

Paediatric population:
See 5.1

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 listed in Appendix V*.

4.9 Overdose

Only limited information is available with regard to human overdose 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

Pharmacotherapeutic group: Carbonic Anhydrase Inhibitor.
ATC code: S 01 EC 03

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).

<Nationally completed name> contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intraocular 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:

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 largescale 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.i.d..

Paediatric Patients
A three month, double-masked, active-treatment controlled, multicentre study was undertaken in 184 (122 for dorzolamide) paediatric patients from one week of age to < 6 years of age with glaucoma or elevated intraocular pressure (baseline IOP > 22 mmHg) to assess the safety of eye drops containing dorzolamide when

administered topically t.i.d. (three times a day). 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 - < 6 years	N = 66 Age range: 2 to 6 years	Timolol 0.5% 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 patients received 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. 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.

In a clinical trial, approximately 26% of patients (20% of patients on dorzolamide monotherapy) were observed to experience product related adverse effects, the majority of which were local, non-serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4% were 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/impairment has been reported.

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 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 substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent 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 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.

In rabbits given maternotoxic doses associated with metabolic acidosis, malformations of the vertebral bodies were observed. In lactating rats, decreases in the body weight gain of offspring were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydroxyethyl cellulose,
mannitol,
sodium citrate,
sodium hydroxide and/or hydrochloride acid (for pH adjustment),
benzalkonium chloride and
purified water

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
As packaged for sale: 2 years
After first opening: 30 days

Chemical and physical in-use stability has been demonstrated for 30 days at 25°C. From a microbiological point of view, once opened, the product may be stored for a maximum of 30 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
As packaged for sale: Store below 30°C. Keep the bottle in the outer carton in order to protect from light.
After first opening: Store below 25°C. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container
Low-density polyethylene bottle fitted with low-density polyethylene dropper tip, polypropylene cap.

5 ml in packs of 1 x 5 ml or 3 x 5 ml or 6 x 5 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements. See section 4.2 for patient instructions.

7. MARKETING AUTHORISATION HOLDER

Bruschettini Srl
Via Isonzo, 6
16147 Genova
Italië

8. MARKETING AUTHORISATION NUMBER(S)

RVG 109493

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 12 oktober 2011
Datum van laatste hernieuwing: 30 oktober 2014

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.4: 20 december 2023