SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DORZOPT 20 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 22.30 mg of dorzolamide hydrochloride equivalent to 20 mg of dorzolamide.
Excipients with known effect: benzalkonium chloride 0.1 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Colourless, slightly viscous, practically free of mechanical impurities, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DORZOPT 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,
• pseudoexfoliative glaucoma.

4.2 Posology and method of administration

Posology

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 drug is being used, the drugs should be administered at least ten minutes apart.

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 be informed of the correct handling of the containers.

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.)

Method of administration

1. Wash your hands.
2. Open the container. Take special care that the tip of the dropper container does not touch your eye, the skin around your eye or your fingers.
3. Tilt your head backwards and hold the container upside down over the eye.
4. Pull the lower eyelid downwards and look up. Hold and gently squeeze the container on the flattened sides of the container and let one drop fall into the space between the lower eyelid and the eye.
5. Press a finger into the corner of your eye, by the nose, or close your eyelids for 2 minutes. This helps to stops the medicine from getting into the rest of the body.
6. Repeat steps 3 to 5 with the other eye if instructed to do so by your doctor.
7. Put the cap back on and close the container tightly.

.

4.3 Contraindications

Hypersensitivity 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 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 and toxic epidermal necrolysis. 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 frequently. 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 (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 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 have been reported after filtration procedures with administration of aqueous suppressant therapies.

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
DORZOPT contains benzalkonium chloride as preservative. 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 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 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 dorzolamide in pregnant women. In rabbits given maternotoxic doses associated with metabolic acidosis, malformations of the vertebral bodies were observed.

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 breast feeding 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 the 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 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 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:
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), Very rare: (<1/10000), or not known (cannot be estimated from the available data).

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.

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.

4.9 Overdose

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

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, ATC code: S01EC03.

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 humour secretion. The result is a reduction in intra-ocular pressure (IOP).

Dorzopt contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular 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 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.

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 similar to 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 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 0.50% 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 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 (twice a day).

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/impairment has 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.

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 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 PARTICULARS

6.1 List of excipients

Hydroxyethylcellulose
Mannitol
Citric acid monohydrate
Sodium hydroxide
Benzalkonium chloride
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening the container, DORZOPT should be used no longer than 28 days.

6.4 Special precautions for storage

Store below 25°C in the original package.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and content of container

5 ml of eye drops solution are packed in a polyethylene bottle, dropper and screw cap sealed with safety ring.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

S.C. Rompharm Company S.R.L.
Eroilor Street, no. 1A, Otopeni, Ilfov County, 075100, Romania

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT