

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Itoco 20 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains dorzolamide hydrochloride equivalent to 20 mg dorzolamide.

Each drop (about 35 µl) contains 0.70 mg of dorzolamide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops)

Clear, colourless, viscous solution.

pH: 5.0 - 6.0

Osmolality: 260 - 310 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Itoco 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

In monotherapy, the dose is 1 drop of dorzolamide in to the conjunctival sac of the affected eye(s), three times daily.

As adjunctive therapy with an ophthalmic beta-adrenolytic, the dose is 1 drop of dorzolamide in the conjunctival sac of the affected eye (eyes) 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 administrated at least 10-minute apart. Eye ointment should be used as the last.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with 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.

Itoco is a sterile solution that does not contain a preservative.

The solution from the bottle (5 ml) can be used for up to 60 days after first opening for administration to the affected eye(s). The solution from the bottle (10 ml) can be used for up to 90 days after first opening for administration to the affected eye(s).

Paediatric population

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

Method of administration

Ocular use.

Before instillation of the eye drops:

- When using for the first time, before delivering a drop to the eye, a patient should first of all practice using the dropper bottle by squeezing it slowly to deliver one drop into the air, away from the eye.
- When a patient is confident that he can deliver one drop at a time, he should choose the position that he finds most comfortable for the instillation of the drops (patient can sit down, lie on his back, or stand in front of a mirror).

Instructions for use:

1. A patient should wash his hands carefully before using this medicine.
2. If the packaging or bottle is damaged the medicine should not be used.
3. When using the medicine for the first time, the cap should be unscrewed after making sure that the sealed ring on the cap has not been broken. A patient should feel a slight resistance until this tamper-proof ring breaks off.
4. If the tamper-proof ring is loose it should be thrown away because it may fall into the eye and make injuries.
5. A patient should tilt his head back and gently pull down his lower eyelid to form a pouch between his eye and eyelid. Contact between the tip of the bottle and eye, eyelids or fingers should be avoided to prevent contamination of the solution.
6. One drop should be instilled into the pouch by pressing slowly on the bottle. A patient should squeeze the bottle gently in the middle and let a drop fall into his eye. There might be a few seconds delay between squeezing and the drop coming out. A patient should not squeeze too hard if he is not sure how to administer this medicine, he should ask doctor, pharmacist or nurse.
7. A patient should close his eye and press the inner corner of the eye with their finger for about two minutes. This helps to stop the medicine from getting into the rest of the body.
8. A patient should repeat steps 5, 6 and 7 in his other eye if the doctor has told him to do this.
9. After use and prior to recapping, the bottle should be shaken once in a downwards direction, without touching the dropper tip, in order to remove any residual liquid on the tip. This is necessary in order to ensure delivery of subsequent drops. After instillation the cap on the bottle should be screwed.

If a drop misses patient's eye, he should try again.

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.

4.3 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 (with creatinine clearance lower than 30 ml/minute) 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 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 (e.g. conjunctivitis and eyelid reactions) are observed, treatment discontinuation 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 dorzolamid (preserved formulation). 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.

Itoco has not been studied in patients wearing 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 following medications without evidence of adverse interactions:

- timolol ophthalmic solution;
- betaxolol ophthalmic solution;
- systemic medications including angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs (including acetylsalicylic acid), and hormones (e.g. oestrogens, 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. No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (See section 5.3).

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 Itoco 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 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

In a multiple-dose, double-masked, active-treatment (dorzolamid multidose) controlled, two period crossover multiclinic study, the safety profile of dorzolamide preservative-free was similar to that of dorzolamide multidose.

Dorzolamide (preserved formulation) was evaluated in more than 1,400 individuals in controlled and uncontrolled clinical studies. In the long term studies in 1,108 patients treated with dorzolamide as monotherapy or as adjunctive therapy with an ophthalmic beta-adrenolytics, the most frequent cause of discontinuations from treatment were drug-related ocular adverse effects in approximately 3% of patients were primarily conjunctivitis and eyelid reactions.

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

[Very Common: ($\geq 1/10$), Common: ($\geq 1/100$ to $< 1/10$), Uncommon: ($\geq 1/1,000$ to $< 1/100$), Rare: ($\geq 1/10,000$ to $< 1/1,000$), 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 the therapy), corneal oedema, ocular hypotony, choroidal detachment following filtration surgery.

Not known: foreign body sensation in eye.

Cardiac disorders:

Not known: palpitations, tachycardia.

Vascular disorders:

Not known: hypertension.

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: astenia/fatigue.

Rare: hypersensitivity – signs and symptoms of a 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.

Paediatric population

See section 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

HPRA Pharmacovigilance

Website: www.hpra.ie

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, 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, 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).

Itoco 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 or accommodative spasm. Dorzolamide has minimal or no effect on pulse rate or blood pressure.

Topically applied beta-adrenolytics agents also reduce the intra-ocular pressure by decreasing aqueous humour secretion but by different mechanism of action. Studies have shown that when dorzolamide is added to a topical beta-adrenolytics, additional reduction in IOP is observed; this findings is consistent with the reported additive effects of beta-adrenolytics and oral carbonic anhydrase inhibitors.

Clinical effects and safety**Adult patients**

In patients with glaucoma or ocular hypertension, the efficacy of dorzolamide used in monotherapy three times a day (baseline IOP ≥ 23 mmHg) or twice a day as adjunctive therapy while receiving ophthalmic beta-adrenolytics (baseline IOP ≥ 22 mmHg) was demonstrated in large-scale clinical studies of up to one-year duration. The IOP-lowering effects 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 treatment to ophthalmic beta-adrenolytics, dorzolamide demonstrated additional IOP similar to pilocarpine 2% used four times a day.

In a multiple-dose, double-masked, active treatment (dorzolamide with preservative) controlled, two period crossover multiclinic study, in 152 patients with elevated baseline intraocular pressure (baseline IOP ≥ 22 mmHg) in one or both eyes, dorzolamide preservative-free had an IOP-lowering effect equivalent to that of dorzolamide with preservative. The safety profile of dorzolamide without preservative was similar to dorzolamide with preservative.

Paediatric population

A 3-month, double-masked, active-treatment controlled, multicenter 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 (preserved-formulation) when administered topically three times a day. Approximately half the patients in both treatment groups were diagnosed with congenital glaucoma; other common etiologies 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 below 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 from 2 to 6 years	n=66 age range: 2 to 6 years	Timolol 0.5% n=35 age range: 2 to 6 years

(*GS – gel solution)

Across both age cohorts approximately 70 patients were treated for 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% three times a day; 30 patients ≥ 2 years were switched to 2% dorzolamide/0.5% timolol fixed combination 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 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%, 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 with dorzolamide, 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 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, malformation 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 a therapeutic dose of dorzolamide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethylcellulose
Mannitol (E421)
Sodium citrate (E331)
Sodium hydroxide (E524) (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, store below 30°C.

Bottle 5 ml
Discard 60 days after the first opening of the bottle.

Bottle 10 ml
Discard 90 days after the first opening of the bottle.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The packaging consists of white LDPE bottles with multidose HDPE dropper applicator with a silicon valve and with tamper-proof HDPE screw-cap, and the carton box.

1 bottle x 5 ml
3 bottles x 5 ml
1 bottle x 10 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Farmaprojects S.A.
Calle Provenca 392 6 Planta
Barcelona
08025
Spain

8 MARKETING AUTHORISATION NUMBER

PA1391/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th August 2022

10 DATE OF REVISION OF THE TEXT

June 2023