1. NAME OF THE MEDICINAL PRODUCT

AZOPT® 10 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 10 mg brinzolamide.
Preservative: 1 ml of suspension contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZOPT eye drops contains brinzolamide, a carbonic anhydrase inhibitor.

AZOPT eye drops is indicated to decrease elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma, as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers.

4.2 Posology and method of administration

Posology

When used as monotherapy or adjunctive therapy, the dose is 1 drop of AZOPT eye drops in the conjunctival sac of the affected eye(s) twice daily. Some patients may have a better response with 1 drop 3 times a day.

When substituting another ophthalmic antiglaucoma agent with AZOPT eye drops, discontinue the other agent and start the following day with AZOPT eye drops.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Use in elderly
No dosage alteration in elderly patients is necessary.

Use in children
The safety and efficacy of AZOPT eye drops in patients below the age of 18 have not been established and its use is not recommended in these patients.

Use in patients with hepatic or renal impairment
AZOPT eye drops has not been studied in patients with hepatic impairment and is therefore not recommended in such patients.

AZOPT eye drops has not been studied in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZOPT eye drops is therefore contraindicated in such patients (see section 4.3).

Method of administration

For ocular use.
Shake well before use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

Nasolacrimal occlusion or gently closing the eyelid after instillation is recommended. This may reduce the systemic absorption of medications administered via the ocular route and result in a decrease in systemic side effects.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known hypersensitivity to sulphonamides (see section 4.4).
- Severe renal impairment.
- Hyperchloraemic acidosis (see section 4.2).

4.4 Special warnings and precautions for use

- Hypersensitivity reactions common to all sulphonamide derivates can occur in patients receiving AZOPT eye drops as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.
- There is limited experience with AZOPT eye drops in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma.
- AZOPT eye drops was primarily evaluated in concomitant administration with timolol during adjunctive glaucoma therapy. Therefore, there are limited data regarding the administration of brinzolamide with other antiglaucomatous agents (see section 4.5).
- AZOPT eye drops has not been studied in patients with narrow-angle glaucoma.
- Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Use with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.
- The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.
- Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZOPT eye drops contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.
- AZOPT eye drops has not been studied in patients wearing contact lenses.
- AZOPT eye drops contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of AZOPT eye drops and wait at least 15 minutes before reinsertion.
- Potential rebound effects following cessation of treatment with AZOPT eye drops have not been studied; the IOP-lowering effect is expected to last for 5-7 days.

- Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination. AZOPT eye drops is absorbed systemically and therefore this may occur with topical administration.

4.5 Interaction with other medicinal products and other forms of interaction

- Specific interaction studies with other medicinal products have not been performed with AZOPT eye drops. In clinical studies, AZOPT eye drops was used concomitantly with prostaglandin analogues and timolol ophthalmic preparations without evidence of adverse interactions. Association between AZOPT eye drops and miotics or adrenergic agonists has not been evaluated during adjunctive glaucoma therapy.
- AZOPT eye drops is a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving AZOPT eye drops.
- 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 AZOPT eye drops. The concomitant administration of AZOPT eye drops and oral carbonic anhydrase inhibitors has not been studied and is not recommended.
- The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, clotrimazole, ritonavir and troleandomycin will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. However, accumulation of brinzolamide is unlikely as renal elimination is the major route. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of ophthalmic brinzolamide in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration (see section 5.3). The potential risk for humans is unknown.

AZOPT eye drops is not recommended during pregnancy.

Breast-feeding
It is unknown whether brinzolamide or its metabolites are excreted in human milk following topical ocular administration; however, a risk to the suckling child cannot be excluded. In animal studies following oral administration, minimal levels of brinzolamide were detected in breast milk.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AZOPT eye drops therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Animal studies with brinzolamide demonstrated no effect on fertility. Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide on human fertility.

4.7 Effects on ability to drive and use machines

AZOPT eye drops has minor influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines (see section 4.8). If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

Additionally, nervous system disorders have been reported with the use of the product which may affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2732 patients treated with AZOPT eye drops as monotherapy or adjunctive therapy to timolol maleate 0.5%, the most frequently reported treatment-related adverse events and local symptoms were: taste perversion (bitter or unusual taste) (6.0%) and temporary blurred vision upon instillation, lasting from a few seconds to a few minutes (5.4%) (see section 4.7).

Tabulated summary of adverse reactions

The following adverse reactions are classified according to the subsequent convention: 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 (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been reported during clinical studies with AZOPT eye drops and post-marketing surveillance.

System Organ Class	Adverse reactions
Metabolism and nutrition disorders	*Not known:* decreased appetite
Psychiatric disorders	*Uncommon:* depression *Rare:* insomnia
Nervous system disorders	*Uncommon:* dizziness, paresthesia, headache *Rare:* memory imparment, somnolence *Not known:* hypoaesthesia
Eye disorders	*Common:* vision blurred, eye irritation, eye pain, ocular discomfort, ocular hyperaemia *Uncommon:* corneal erosion, punctate keratitis, keratitis, keratopathy, conjunctivitis, conjunctivitis allergic, blepharitis, photophobia, dry eye, asthenopia, abnormal vision, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting *Rare:* corneal oedema, diplopia, visual acuity reduced, photopsia, hypoaesthesia eye, periorbital oedema, conjunctival follicles
Ear and labyrinth disorders	*Rare:* tinnitus
Cardiac disorders	*Rare:* angina pectoris, heart rate irregular
Vascular disorders	*Not known:* blood pressure decreased
Respiratory, thoracic and mediastinal disorders	*Uncommon*: bronchitis, dyspnoea, epistaxis, haemoptysis, rhinitis, rhinorrhoea, oropharyngeal pain, upper airway cough syndrome, throat irritation *Rare*: bronchial hyperreactivity, upper-respiratory tract congestion, sinus congestion, nasal congestion, cough, nasal dryness, pharyngitis
Gastrointestinal disorders	*Common:* dysgeusia *Uncommon:* nausea, diarrhoea, dyspepsia, abdominal discomfort, dry mouth
Skin and subcutaneous tissue disorders	*Uncommon:* rash, dermatitis *Rare*: urticaria, alopecia, pruritus generalised
Musculoskeletal and connective tissue disorders	*Not known:* arthralgia
General disorders and administration site conditions	*Uncommon:* fatigue

	Rare: chest pain, feeling jittery, asthenia, irritability

Description of selected adverse reactions

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic adverse reaction associated with the use of AZOPT eye drops during clinical trials. It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is attributable to brinzolamide. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

AZOPT eye drops contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same type of adverse reactions attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

4.9 Overdose

A topical overdose of AZOPT eye drops may be flushed from the eye(s) with lukewarm water.

No case of overdose has been reported.

Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, carbonic anhydrase inhibitors.
ATC code: S01EC04.

Mechanism of action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body, including the eye. Carbonic anhydrase catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid.

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) which is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Brinzolamide is an inhibitor of carbonic anhydrase II (CA-II), the predominant iso-enzyme in the eye, with an *in vitro* IC_{50} of 3.2 nM and a K_i of 0.13 nM against CA-II.

Clinical efficacy and safety

The IOP-reducing effect of AZOPT eye drops as adjunctive therapy to the prostaglandin analogue travoprost was studied. Following a 4 week run-in with travoprost, patients with an IOP ≥19 mmHg were randomized to receive added treatment with brinzolamide or timolol. An additional decrease in mean diurnal IOP of 3.2 to 3.4 mmHg for the brinzolamide group and 3.2 to 4.2 mmHg for the timolol group were observed. There was an overall higher incidence of non-serious ocular adverse reactions, mainly related to signs of local irritation, in the brinzolamide/travoprost groups. The events were mild and did not affect the overall discontinuation rates in the studies.

A clinical trial was conducted with AZOPT eye drops in 32 paediatric patients less than 6 years of age, diagnosed with glaucoma or ocular hypertension. Some patients were naive to IOP therapy whilst others were on other IOP-lowering medicinal product(s). Those who had been on previous IOP medicinal

product(s) were not required to discontinue their IOP medicinal product(s) until initiation of monotherapy with AZOPT eye drops.

Among patients who were naive to IOP therapy (10 patients), the efficacy of AZOPT eye drops was similar to that seen previously in adults, with mean IOP reductions from baseline ranging up to 5 mmHg. Among patients who were on topical IOP-lowering medicinal product(s) (22 patients), mean IOP increased slightly from baseline in the AZOPT eye drops group.

5.2 Pharmacokinetic properties

Absorption

After ocular administration of AZOPT eye drops, brinzolamide is systemically absorbed and due to its high affinity for CA-II accumulates in circulating red blood cells (RBCs) with a half-life of 111 days. RBC concentration of brinzolamide after long term oral and ocular administration reaches a saturable mean concentration at approximately 20 μM. This brinzolamide concentration is similar to the RBC concentration (22-27 μM) attained after oral dosing of brinzolamide in a pharmacokinetic study where healthy volunteers received 1-mg capsules of brinzolamide twice daily for up to 32 weeks and RBC CA activity was measured to assess the degree of systemic CA inhibition. In addition, the metabolite N-desethyl brinzolamide also binds to CA and accumulates in RBCs after ocular and oral administration. However, the degree of carbonic anhydrase inhibition at these saturable levels is not sufficient for systemic effects. In addition, brinzolamide and N-desethyl brinzolamide concentration in plasma after topical ocular dosing of AZOPT eye drops was typically near or below the limit of quantitation (7.5 ng/ml).
Subjects with moderate renal impairment (creatinine clearance of 30-60 ml/minute) were administered 1 mg of brinzolamide twice daily orally for up to 54 weeks. Brinzolamide RBC concentration ranged from about 20 to 40 μM by week 4 of treatment. At steady-state, brinzolamide and its metabolite RBC concentrations ranged from 22.0 to 46.1 and 17.1 to 88.6 μM, respectively. N-desethyl brinzolamide RBC concentrations increased and total RBC CA activity decreased with decreasing creatinine clearance but brinzolamide RBC concentrations and CA-II activity remained unchanged.

Distribution

Brinzolamide moderately binds to human plasma proteins (~60%); therefore the risk of drug interactions with compounds that also bind to plasma proteins is low. Brinzolamide moderately binds to melanin based on pigmented and non-pigmented rabbit studies. However, the half-life of brinzolamide in rabbit tissues is more influenced by its RBC binding than melanin binding.
Brinzolamide is distributed to ocular tissues after topical dosing of AZOPT eye drops to rabbits. After single topical doses, the higher concentrations are found in the anterior tissues compared to posterior tissues; whereas after multiple dosing, drug accumulates in many ocular tissues, due to its high affinity and tight binding to carbonic anhydrase II enzymes. This results in long half-lives in iris-ciliary body, choroid, retina, and lens which are similar to the half-life in blood (except in the lens which resulted in longer half-life than in blood). After multiple dosing, the accumulation of brinzolamide in posterior tissues such as retina and choroid is the result of blood circulation in these tissues, which result in long T_{max} as well as a long half-life. In contrast, aqueous humor, vitreous humor and plasma have relatively short half-lives and accumulation is absent after BID or TID dosing, which is the result from the lack of carbonic anhydrases in these tissues.

Metabolism

N-desethyl brinzolamide is the major human metabolite found in blood and urine. This metabolite is also a known inhibitor of carbonic anhydrase. Cytochrome P-450 CYP3A4 is the major enzyme responsible for the formation of this metabolite; however, additional P-450s appear to contribute to brinzolamide's clearance. Brinzolamide exhibits no inhibition of P-450s at concentrations up to and including 1000 ng/ml, which is more than 100-fold higher than those in human plasma at steady state. In addition to N-desethyl brinzolamide, other metabolites; O-desmethyl brinzolamide and N-desmethoxypropyl brinzolamide also have been detected in human urine. These metabolites are not specific to humans and have been identified in nonclinical species after oral brinzolamide administration. The isomerization of the R-enantiomer to the Senantiomer has not been observed.

Elimination

Brinzolamide is predominantly cleared by the kidney as unchanged drug (60%). About 20% of the dose has been accounted for in urine as metabolite.

5.3 Preclinical safety data

Non-clinical data on brinzolamide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

Topical ocular administration of brinzolamide to rabbits for one to six months resulted in slight, statistically significant increases in corneal thickness when given at concentrations of 1%, 2% and 4%, four times a day; these changes were not observed in other species. Chronic administration of brinzolamide to rats at a dose level of 8 mg/kg/day (up to 250 times the recommended human ophthalmic dose) resulted in changes associated with the pharmacology of carbonic anhydrase inhibition (i.e., urine volume and electrolyte changes, slight differences in serum electrolytes).

A statistically significant increase in urinary bladder tumours was observed in female mice given brinzolamide 10 mg/kg/day (250 times the recommended human ophthalmic dose), orally, for 24 months. Dose-related proliferative changes in the urinary bladder were observed among female mice at 1, 3 and 10 mg/kg/day, and among males at 3 and 10 mg/kg/day. The elevated bladder tumour incidence, which was statistically significant, was primarily due to the increased incidence of a tumour considered unique to mice.

Developmental toxicity studies in rabbits with oral doses of brinzolamide of up to 6 mg/kg/day (125 times the recommended human ophthalmic dose) revealed no effect on foetal development despite significant maternal toxicity. Similar studies in rats resulted in slightly reduced ossification of skull and sternebrae of foetuses of dams receiving brinzolamide at doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose), but not 6 mg/kg/day. These findings occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. Dose-related decreases in foetal weights were observed in pups of dams receiving brinzolamide orally ranging from a slight decrease (about 5-6%) at 2 mg/kg/day to nearly 14% at 18 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid/sodium hydroxide (to adjust pH) and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store at 4° to 30°C (39° to 86°F).
Discard 4 weeks after first opening.
Do not use this medicine after the expiry date which is stated on the packaging.
Keep out of the reach and sight of children.

6.4 Nature and contents of container

5 ml natural low density polyethylene bottles with polypropylene screw caps (DROP-TAINER®).

The following pack sizes are available: outer cartons containing 1 x 5 ml and 3 x 5 ml bottles.
Not all pack sizes may be marketed.

6.5 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured by:

ALCON-COUVREUR
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