NOVARTIS

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.
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 contain brinzolamide, a carbonic anhydrase inhibitor.
AZOPT eye drops is indicated to decrease elevated intraocular pressure (IOP) in adult 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. Eye ointments should be administered last.

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 impairment

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

Use in patients with renal impairment

AZOPT eye drops has not been studied in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m^2) 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 also 4.3). However, in patients with moderate renal impairment (creatinine clearance 30-60 mL/min/1.73 m^2) there is no need for dose adjustments with topical administration of brinzolamide 1%.

Method of administration

For ocular use

Shake well before use.

After cap is removed, if tamper evident snap collar is loose, this should be removed before using the product

To avoid contamination, the dropped tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

Nasolacrimal occlusion and closing the eyelid for 2 minutes after instillation is recommended. This may result in a decrease in systemic side effects and an increase in local activity.

Patients must be instructed to remove soft contact lenses prior to application of Azopt, and to wait 15 minutes after instillation of the dose before reinsertion.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

- Like other topically applied ophthalmic agents, brinzolamide is absorbed systemically. Systemic absorption can be minimised by nasolacrimal occlusion (see section 4.2 Method of administration).
- AZOPT is a sulphonamide and, although administered topically, it is absorbed systemically. Therefore, the same types of undesirable effects that are attributable to sulphonamides may occur with topical administration. Hypersensitivity reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can occur. At the time of prescription,

patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs of serious reactions or hypersensitivity occur, use of this product should be discontinued immediately.

- 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. Azopt should be used 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. Carbonic anhyrase inhibitors may affect corneal hydration, which may lead to corneal decompensation and edema. Wearing contact lenses, might hence 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.
- Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Patients should avoid contact with soft contact lenses. Patients must be instructed to remove contact lens prior to application of AZOPT eye drops and to 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 (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates) 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 adequate and well-controlled studies in pregnant women regarding the ocular use of Azopt.

In reproductive toxicity studies, brinzolamide administered orally to rats during organogenesis induced fetal toxicity at 375 times the maximum recommended ophthalmic human dose (MROHD) based on body weight (BW). In rabbits, no fetal toxicity was observed following oral administration during organogenesis at 125 times the MROHD based on BW (See Animal data).

Azopt should not be used during pregnancy unless clearly necessary.

Animal data

Embryofetal development studies were conducted in pregnant rats administered 0, 2, 6 or 18 mg/kg/day brinzolamide by oral gavage on gestation days 6 to 17 to target the period of organogenesis. Decreased maternal weight gain was observed at 6 and 18 mg/kg/day. Decreased fetal body weight and reduced skeletal ossification were observed at 18 mg/kg/day (375 times the MROHD based on BW and 60 times the MROHD based on Body Surface Area (BSA)). The No-Observed Effect Level (NOEL) was 2 mg/kg/day (42 times the MROHD based on BW and 7 times the MROHD based on BSA).

Embryofetal development studies were conducted in pregnant rabbits administered 0, 1, 3, or 6 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Maternal weight loss during pregnancy was observed at 3 mg/kg/day (63 times the MROHD based on BW and 20 times the MROHD based on BSA) and above. At 6 mg/kg/day, mortality, emaciation, lack of feces and abortions were noted in does. The NOEL for maternal toxicity was 1 mg/kg/day (21 times the MROHD based on BW and 7 times the MROHD based on BSA). No treatment-related fetal effects were observed up to the maximum tested dose of 6 mg/kg/day (125 times the MROHD based on BW and 41 times the MROHD based on BSA).

In a rat peri-/postnatal study, brinzolamide was orally administered at doses of 1, 5 and 15 mg/kg/day from gestation day 16 through lactation day 20. Decreases in food consumption and mean body weight gain was seen in parental dams during gestation and lactation at 15 mg/kg/day. Decreased pup body weight was observed at 15 mg/kg/day (313 times the MROHD based on BW and 51 times the MROHD based on BSA). The NOEL for maternal and developmental toxicity was 5 mg/kg/day (104 times the MROHD based on BW and 17 times the MROHD based on BSA).

Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and the levels of radioactivity in fetal tissues were 3- to 10-fold less than those measured in the dams.

The potential risk for humans is unknown.

Breast-feeding

There are no adequate data regarding the use of Azopt in breast-feeding womenThere are no data regarding the effects of brinzolamide on the breastfed infant, or milk production.

It is not known whether brinzolamide is transferred into human milk following topical ocular administration. Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Azopt and any potential adverse effects on the breast-fed child from Azopt.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Azopt on human fertility. In a rat fertility study, no adverse effects on the fertility or reproductive capacity of males or females were observed at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose based on BW and 60 times the MROHD based on BSA).

No effects on male or female fertility are anticipated from the use of Azopt.

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

In clinical studies involving 2732 patients treated with AZOPT 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 (≥1/1000 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 the 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, irregular heart rate
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 *Not known*: Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)
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 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), which is 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.

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, it 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, 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

Plasma protein binding of brinzolamide is moderate (about 60 %). Brinzolamide is sequestered in RBCs due to its high affinity binding to CA-II and to a lesser extent to CA-I. Its active N-desethyl metabolite also accumulates in RBCs where it binds primarily to CA-I. The affinity of brinzolamide and metabolite to RBC and tissue CA results in low plasma concentrations.

Metabolism

The metabolic pathways for the metabolism of brinzolamide involve N-dealkylations, O-dealkylations and oxidation of its N-propyl side chain. N-desethyl brinzolamide is a major metabolite of brinzolamide formed in humans, which also binds to CA-I in the presence of brinzolamide and accumulates in RBCs. In vitro cytochrome P450 isozyme studies show that the metabolism of brinzolamide mainly involves CYP3A4 as well as at least four other isozymes, which include CYP2A6, CYP2B6, CYP2C8 and CYP2C9.

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 single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, and topical ocular irritation studies. For information on reproductive and developmental toxicity, see section Fertility, pregnancy and lactation.

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, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide (to adjust pH) and/or hydrochloric acid, 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. AZOPT must be kept out of the sight and reach of children.

6.4 Nature and content of container

5 ml natural low density polyethylene bottles with polypropylene screw caps.

The following pack sizes are available: outer cartons containing 1 x 5 ml, 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.

6.6 Manufacturer
See folding box

Novartis Pharma AG, Basel, Switzerland