NOVARTIS

BRINZOLAMIDE

AZOPT®
10 mg/mL (1%)
Sterile Ophthalmic Suspension
Anti-Glaucoma

DESCRIPTION AND COMPOSITION

Pharmaceutical form

White to off-white Sterile Ophthalmic Suspension.

Active substance

Each mL of suspension contains:
Brinzolamide.....10 mg

Excipients

Excipient with known effect: 1 mL of the sterile ophthalmic suspension contains 0.1 mg of benzalkonium chloride.

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

Pharmaceutical formulations may vary between countries.

INDICATIONS

Brinzolamide (Azopt®) Sterile Ophthalmic Suspension is a carbonic anhydrase inhibitor indicated to decrease elevated intraocular pressure (IOP) in adult patients with ocular hypertension or open-angle glaucoma, as monotherapy in adult patients unresponsive to beta-blockers or in adult patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers or prostaglandin analogues.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Adults

The dosing of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension for the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma is one drop in the affected eye(s) 3 times daily.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) 3 times daily.

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

Special populations

Renal impairment

Brinzolamide has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2). Since brinzolamide and its major metabolite are excreted predominately by the kidney, brinzolamide is therefore contraindicated in such patients. 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%.

Hepatic impairment

Brinzolamide (Azopt®) Sterile Ophthalmic Suspension has not been studied in patients with hepatic impairment and is therefore not recommended in such patients.

Pediatric patients (below 18 years)

The safety and efficacy of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension in patients below the age of 18 have not been established and its use is not recommended in these patients.

Geriatric patients (65 years of age or above)

No overall differences in safety or effectiveness have been observed between elderly and younger patients. No dose adjustment in elderly patients is necessary.

Method of administration

- For ocular use.
- Patients should be instructed to shake the bottle well before use.
- To avoid contamination, the dropper 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension and to wait 15 minutes after instillation of the dose before reinsertion.
- After cap is removed, if tamper evident snap collar is loose, this should be removed before using the product.

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to any of the excipients or to sulphonamides.
- Severe renal impairment.
- Hyperchloraemic acidosis.

WARNINGS AND PRECAUTIONS

General

Like other topically applied ophthalmic agents, brinzolamide is absorbed systemically. Systemic

absorption can be minimized by nasolacrimal occlusion (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving Brinzolamide (Azopt®) Sterile Ophthalmic Suspension as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, use of this product should be discontinued.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Brinzolamide (Azopt®) Sterile Ophthalmic Suspension 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). Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and edema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Contact lenses

Benzalkonium chloride may cause eye irritation and is known to discolor soft contact lenses. Patients should avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension, and to wait at least 15 minutes before reinsertion.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Psychiatric disorders	Depression	Uncommon
	Insomnia	Rare
Nervous system disorders	Dizziness, paresthesia, headache	Uncommon
	Memory impairment, somnolence	Rare
Eye disorders	Vision blurred, eye irritation, eye pain, ocular discomfort, ocular hyperaemia	Common
	Corneal erosion, punctate keratitis, keratitis, conjunctivitis, conjunctivitis allergic, blepharitis, photophobia, dry eye, asthenopia, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting	Uncommon
	Corneal oedema, diplopia, visual acuity reduced, photopsia, hypoaesthesia eye, periorbital oedema	Rare
Ear and labyrinth disorders	Tinnitus	Rare

Cardiac disorders	Angina pectoris, irregular heart rate	Rare

System organ classification	Adverse drug reaction	Frequency category
Respiratory, thoracic and mediastinal disorders	Dyspnoea, epistaxis, rhinorrhoea,oropharyngeal pain, upper airway cough syndrome, throat irritation	Uncommon
	Bronchial hyperreactivity, upper-respiratory tract congestion, sinus congestion, nasal congestion, cough, nasal dryness	Rare
Gastrointestinal disorders	Dysgeusia	Common
	Nausea, diarrhoea, dyspepsia, abdominal discomfort, dry mouth	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Urticaria, alopecia, pruritus generalised	Rare
General disorders and administration site conditions	Fatigue	Uncommon
	chest pain, feeling jittery, asthenia, irritability	Rare

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Brinzolamide (Azopt®) Sterile Ophthalmic Suspension via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Hypoaesthesia
Vascular disorders	Blood pressure decreased
Musculoskeletal and connective tissue disorders	Arthralgia

INTERACTIONS

The following interactions are expected with Brinzolamide (Azopt®) Sterile Ophthalmic Suspension:

Brinzolamide (Azopt®) Sterile Ophthalmic Suspension 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. nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates) must be considered in patients receiving Brinzolamide (Azopt®) Sterile Ophthalmic Suspension. 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension. The concomitant administration of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension and oral carbonic anhydrase inhibitors is not recommended.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well controlled studies in pregnant women regarding the ocular use of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension.

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).

Brinzolamide (Azopt®) Sterile Ophthalmic Suspension should not be used during pregnancy unless clearly necessary.

Data

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.

Lactation

Risk summary

There are no adequate data regarding the use of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension in breast-feeding women.

There 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension and any potential adverse effects on the breast-fed child from Brinzolamide (Azopt®) Sterile Ophthalmic Suspension.

Females and males of reproductive potential

Infertility

Studies have not been performed to evaluate the effect of topical ocular administration of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension.

OVERDOSAGE

No specific reactions are to be expected with an ocular overdose of the product. In case of accidental ingestion, 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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

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.

Pharmacokinetics (PK)

Absorption

After ocular administration of Brinzolamide (Azopt®) 10 mg/mL (1%) Sterile Ophthalmic Suspension, brinzolamide is systemically absorbed and accumulates in circulating red blood cells (RBCs) with a half-life of 111 days. RBCs concentration of brinzolamide after long term oral and ocular administration reaches a saturable mean concentration of 20 μM. This brinzolamide concentration is similar to the RBC concentration (22-27 μM) attained after oral dosing of brinzolamide, 1 mg BID for 32 weeks. In addition, the metabolite N-desacetyl brinzolamide also 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-desacetyl brinzolamide concentration in plasma after topical ocular dosing of Brinzolamide (Azopt®) 10 mg/mL (1%) Sterile Ophthalmic Suspension was typically near or below the limit of quantitation.

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 bind 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 Brinzolamide (Azopt®) 10 mg/mL (1%) Sterile Ophthalmic Suspension 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.

Biotransformation/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; additional P-450s appear to contribute to brinzolamide's clearance as well. Brinzolamide exhibits no inhibition of P-450s at concentrations up to and including 1000ng/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 human and have been identified in non-clinical species after oral brinzolamide administration as well. The isomerization of the R enantiomer to the S-enantiomer has not been observed.

Elimination

Brinzolamide is predominately cleared by the kidney as unchanged drug (60%) and other 20% is excreted in the urine as metabolites.

CLINICAL STUDIES

The IOP-reducing effect of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension in 32 pediatric 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension. Among patients who were naive to IOP therapy (10 patients), the efficacy of Brinzolamide (Azopt®) Sterile Ophthalmic Suspension 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 Brinzolamide (Azopt®) Sterile Ophthalmic Suspension group.

NON-CLINICAL 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 PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable.

STORAGE

Store Brinzolamide (Azopt®) 10 mg/ml (1%) Sterile Ophthalmic Suspension at a temperature not exceeding 25°C.
Discard 4 weeks after first opening.
This medicinal product does not require any special storage conditions.
Brinzolamide (Azopt®) Sterile Ophthalmic Suspension should not be used after the date marked “EXP” on the pack.
Brinzolamide (Azopt®) Sterile Ophthalmic Suspension must be kept out of the sight and reach of children.

Availability

LDPE Plastic Bottle x 5 mL (Box of 1’s)

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Special precautions for disposal

No special requirements.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reactions, report to the FDA: www.fda.gov.ph

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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® = registered trademark

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