

PRODUCT MONOGRAPH

^{Pr} **AZARGA™**
brinzolamide and timolol maleate
ophthalmic suspension
brinzolamide 1.0% and timolol 0.5% (as timolol maleate)

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor and Topical Beta-Adrenergic Blocking Agent)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic (topical)	Suspension / brinzolamide 1.0% and timolol 0.5% (as timolol maleate)	benzalkonium chloride <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

AZARGA™ (brinzolamide/timolol) ophthalmic suspension is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction and when the combination therapy is appropriate.

Geriatrics (> 65 years of age):

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Pediatrics (< 18 years of age):

The safety and effectiveness of AZARGA™ suspension in pediatric patients have not been established. Its use is not recommended in these patients until further data become available.

CONTRAINDICATIONS

- hypersensitivity to brinzolamide, timolol, or to any ingredient in the formulation or component of the container (for a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph)
- bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock

- severe allergic rhinitis and bronchial hyper-reactivity; hypersensitivity to other beta-blockers
- hyperchloraemic acidosis
- severe renal impairment
- hypersensitivity to sulfonamides

No studies have been conducted with AZARGA™ (brinzolamide/timolol) ophthalmic suspension or timolol maleate ophthalmic solution in patients with hepatic or renal impairment, or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA™ suspension is therefore contraindicated in patients with severe renal impairment.

WARNINGS AND PRECAUTIONS

General

Like other topically applied ophthalmic agents, brinzolamide and timolol are absorbed systemically.

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. Cardiac failure should be adequately controlled before beginning therapy with AZARGA™ (brinzolamide/timolol) ophthalmic suspension. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely, death in association with cardiac failure, have been reported following administration of timolol maleate.

Beta adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile insulin-dependent diabetes as beta adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Timolol may interact with other medicinal products.

The effect on intraocular pressure or the known effects of systemic beta blockade may be potentiated when AZARGA™ suspension is given to patients already receiving an oral beta-adrenergic blocking agent. The use of two local beta-adrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended.

AZARGA™ suspension contains brinzolamide, a sulphonamide. The same type of undesirable effects that are attributable to sulphonamides may occur with topical administration. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. If signs of serious reactions or hypersensitivity occur, discontinue the use of this medicinal product.

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZARGA™ suspension. The concomitant administration of AZARGA™ suspension and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Hepatic

AZARGA™ suspension has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

Immune

Anaphylactic Reactions

While taking beta adrenergic blocking agents, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Ophthalmologic

There is limited experience with AZARGA™ suspension in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma.

AZARGA™ suspension has not been studied in patients with narrow-angle glaucoma.

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial 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. Likewise, in other cases of compromised corneas such as patients with diabetes mellitus, careful monitoring is recommended.

AZARGA™ suspension contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of AZARGA™ suspension and wait 15 minutes after instillation of the dose before reinsertion.

As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Special Populations

Pregnant Women:

There are no adequate data from the use of brinzolamide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Well-controlled epidemiological studies with systemic use of beta adrenergic blocking agents did not indicate malformation effects, but some pharmacological effects such as bradycardia have been observed in fetuses or neonates. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in ophthalmic solutions on pregnancy or on the health of the fetus/newborn child but bradycardia and arrhythmia have been reported in one case in the fetus of a woman treated with timolol ophthalmic solution. To date, no other relevant epidemiological data are available.

AZARGA™ suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women:

It is not known whether brinzolamide is excreted in human breast milk. Animal studies have shown excretion of brinzolamide in breast milk. Timolol does appear in breast milk. However, at therapeutic doses of timolol in ophthalmic solutions, the calculated dose of timolol for the nursing child would be too low to produce clinical beta-blockade.

Because of the potential for serious adverse reactions from AZARGA™ suspension in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):

Safety and effectiveness of AZARGA™ suspension in children have not been established.

Geriatrics (> 65 years of age):

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination in elderly patients. AZARGA™ suspension is absorbed systemically and therefore this may occur with topical administration in elderly patients.

Monitoring and Laboratory Tests

No untoward safety issues were identified based upon a review of the laboratory data (haematology, blood chemistry, and urinalysis) from a single pharmacokinetic study.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies involving over 500 patients treated with AZARGA™ (brinzolamide/timolol) ophthalmic suspension, the most frequently reported adverse drug reaction was temporary blurred vision (6%) upon instillation, lasting from a few seconds to a few minutes.

Dysgeusia (bitter or unusual taste in the mouth following topical ocular instillation) was the most frequently reported systemic adverse drug reaction. It is likely caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is attributable to the brinzolamide

component of this combination product. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the incidence of this effect.

AZARGA™ suspension 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 drug reactions that are attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 5 clinical studies, AZARGA™ suspension was administered to 501 patients at a dose of one drop two times daily for up to 1 year. The most frequent adverse drug reactions ($\geq 1\%$) seen in clinical trials are presented in Table 1.

Table 1: Treatment-Related Adverse Drug Reactions $\geq 1\%$

MedDRA Preferred Term (Version 10.0)	AZARGA™ N = 501 (%)	COSOPT* N = 264 (%)	AZOPT® N = 203 (%)	Timolol N = 236 (%)
Eye Disorders				
blurred vision	6%	1%	3%	1%
eye irritation	4%	12%	2%	3%
eye pain	3%	9%	0%	1%
foreign body sensation in eyes	1%	0%	0%	0%
Nervous System Disorders				
dysgeusia	2%	2%	5%	0%

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye disorders: conjunctival hyperaemia, eye pruritus, intraocular pressure decreased, ocular hyperaemia, punctuate keratitis, dry eye, eye discharge, abnormal sensation in eye, anterior chamber flare, asthenopia, blepharitis, blepharitis allergic, conjunctivitis allergic, corneal disorder, corneal erosion, eyelid margin crusting, eyelids pruritus, erythema of eyelid, lacrimation increased, photophobia, scleral hyperaemia; **Psychiatric disorders:** insomnia
Respiratory, thoracic and mediastinal disorders: chronic obstructive pulmonary disease, cough, pharyngolaryngeal pain, rhinorrhoea; **Skin and subcutaneous tissue disorders:** hair disorder, lichen planus; **Vascular disorders:** blood pressure decreased

Additional Adverse Reactions Observed with the Individual Components of AZARGA™ Suspension

AZARGA™ suspension contains brinzolamide and timolol (as timolol maleate). Additional adverse reactions associated with the use of the individual components observed in clinical studies that may potentially occur with AZARGA™ suspension include:

Brinzolamide 1.0% (Clinical trials)

Blood and the lymphatic system disorders: blood chloride increased, red blood cell count decreased; **Cardiac disorders:** angina pectoris, arrhythmia, bradycardia, cardio-respiratory distress, heart rate increased, heart rate irregular, palpitation, tachycardia; **Ear and labyrinth disorders:** tinnitus, vertigo; **Eye disorders:** conjunctivitis, corneal epithelium defect, corneal epithelium disorder, corneal staining, corneal oedema, deposit eye, diplopia, eye allergy, eye swelling, eyelid disorder, eyelid oedema, glare, hypoaesthesia eye, intraocular pressure increased, keratitis, keratoconjunctivitis sicca, keratopathy, madarosis, meibomianitis, ocular discomfort, optic nerve cup/disc ratio increased, photopsia, pterygium, scleral pigmentation, subconjunctival cyst, visual acuity reduced, visual disturbance; **Gastrointestinal disorders:** abdominal discomfort, diarrhea, dry mouth, dyspepsia, flatulence, frequent bowel movements, gastrointestinal disorder, hypoaesthesia oral, nausea, oesophagitis, paraesthesia oral, stomach discomfort, upper abdominal pain, vomiting; **General disorders and administration site conditions:** asthenia, chest discomfort, chest pain, fatigue, feeling abnormal, feeling jittery, irritability, malaise, medication residue, pain, peripheral oedema; **Hepatobiliary disorders:** liver function test abnormal; **Immune system disorders:** hypersensitivity; **Infections and infestations:** nasopharyngitis, pharyngitis, rhinitis, sinusitis; **Injury, poisoning and procedural complications:** foreign body in eye; **Musculoskeletal and connective tissue disorders:** arthralgia, back pain, muscle spasms, myalgia, pain in extremity; **Nervous system disorders:** ageusia, amnesia, dizziness, headache, hypoaesthesia, motor dysfunction, memory impairment, paraesthesia, somnolence, tremor; **Psychiatric disorders:** apathy, depressed mood, depression, libido decreased, nervousness, nightmare; **Renal and urinary disorders:** pollakiuria, renal pain; **Reproductive system and breast disorders:** erectile dysfunction; **Respiratory, thoracic and mediastinal disorders:** asthma, bronchial hyperactivity, dyspnoea, epistaxis, nasal congestion, nasal dryness, postnasal drip, sneezing, throat irritation, upper respiratory tract congestion; **Skin and subcutaneous tissue disorders:** alopecia, dermatitis, erythema, pruritus generalized, rash, rash maculo-papular, skin tightness, urticaria; **Vascular disorders:** blood pressure increased, hypertension

Timolol 0.5% (Clinical trials)

Cardiac disorders: arrhythmia, atrioventricular block, bradycardia, cardiac arrest, cardiac failure, palpitation; **Eye disorders:** conjunctivitis, diplopia, eyelid ptosis, keratitis, visual disturbance; **Gastrointestinal disorders:** diarrhoea, nausea; **General disorders and administration site conditions:** asthenia, chest pain; **Metabolism and nutrition disorders:** hypoglycemia; **Nervous system disorders:** cerebral ischaemia, cerebrovascular accident, dizziness, headache, myasthenia gravis, paresthesia, syncope; **Psychiatric disorders:** depression; **Respiratory, thoracic and mediastinal disorders:** bronchospasm, dyspnoea, nasal congestion, respiratory failure; **Skin and subcutaneous tissue disorders:** alopecia, rash; **Vascular disorders:** hypotension

Abnormal Hematologic and Clinical Chemistry Findings

AZARGA™ suspension had no clinically relevant treatment-related effect on laboratory parameters.

Post-Market Adverse Drug Reactions

Adverse reactions identified from post-marketing experience with the individual components that have not been reported previously in clinical trials with AZARGA™ suspension, brinzolamide 1.0% or timolol 0.5% are listed below.

Brinzolamide 1.0% (Post-marketing)

Blood and the lymphatic system disorders: agranulocytosis, thrombocytopenia; **Cardiac disorders:** cardiac disorder, supraventricular extrasystoles; **Congenital and familial/genetic disorders:** congenital anomaly; **Ear and labyrinth disorders:** ear pain; **Eye disorders:** corneal opacity, iris disorder, periorbital disorder, accommodation disorder, anterior chamber fibrin, blepharospasm, choroidal detachment, conjunctival haemorrhage, conjunctival irritation, conjunctival oedema, conjunctival scar, corneal degeneration, dark circles under eyes, descemet's membrane disorder, eye oedema, eyelid exfoliation, iritis, macular oedema, ocular vascular disorder, oculogyration, optic disc drusen, uveitis, visual brightness; **Gastrointestinal disorders:** abdominal pain, mouth haemorrhage, dysphagia, pancreatitis acute; **General disorders and administration site conditions:** drug intolerance, drug ineffective, condition aggravated, adverse drug reaction, face oedema, facial pain, feeling cold, pyrexia, sensation of foreign body; **Hepatobiliary disorders:** jaundice; **Immune system disorders:** anaphylactic shock; **Injury, poisoning and procedural complications:** injury, limb injury, drug exposure during pregnancy, periorbital haematoma, transplant failure; **Infections and infestations:** bronchitis, herpes ophthalmic, herpes virus infection, pneumonia; **Investigations:** gamma-glutamyltransferase increased, hepatic enzyme increased, blood lactic acid increased, blood urea increased, body temperature decreased, electrocardiogram abnormal; **Metabolism and nutrition disorders:** metabolic acidosis, anorexia; **Musculoskeletal and connective tissue disorders:** musculoskeletal discomfort; **Nervous system disorders:** hypogeusia, hyposmia, anosmia, aphonia, burning sensation, burning sensation mucosal, cerebral infarction, cerebrovascular accident, convulsion, disturbance in attention, facial palsy, hyperaesthesia, lethargy, loss of consciousness; **Psychiatric disorders:** anxiety, agitation, bradyphrenia, depressive symptom, fear, restlessness, thought blocking; **Renal and urinary disorders:** micturition disorder, micturition urgency, renal failure acute; **Respiratory, thoracic and mediastinal disorders:** bronchospasm, dry throat, dysphonia, lung disorder, nasal discomfort, nasal turbinate abnormality, respiratory distress, respiratory failure; **Skin and subcutaneous tissue disorders:** pruritus, dermatitis contact, eczema, hyperhidrosis, dry skin, hair colour changes, hair texture abnormal, periorbital oedema, psoriasis, rash generalised, rash pruritic, rash vesicular, skin hyperpigmentation, skin reaction, swelling face, vascular purpura; **Surgical and medical procedures:** sinus operation; **Vascular disorders:** angiopathy, haematoma, hot flush

Timolol 0.5% (Post-marketing)

Cardiac disorders: atrioventricular block complete, accelerated idioventricular rhythm, cardiotoxicity, myocardial infarction, sinus bradycardia; **Congenital and familial/genetic disorders:** multiple congenital abnormalities; **Ear and labyrinth disorders:** vertigo; **Endocrine disorders:** thyroid disorder; **Eye disorders:** visual acuity reduced, corneal deposits,

conjunctival oedema, corneal oedema, corneal opacity, corneal scar, ectropion, eye allergy, eye disorder, keratopathy, miosis; **General disorders and administration site conditions:** chest discomfort, drug ineffective, drug interaction, fatigue, peripheral coldness, tachyphylaxis; **Immune system disorders:** hypersensitivity; **Infections and infestations:** nasopharyngitis; **Injury, poisoning and procedural complications:** accidental exposure, drug exposure during pregnancy, fall, medication error, transplant failure; **Investigations:** heart rate increased, blood phosphorus increased, pulse abnormal, respiratory rate increased, skin test positive; **Metabolism and nutrition disorders:** metabolic acidosis; **Musculoskeletal and connective tissue disorders:** muscular weakness, myalgia; **Nervous system disorders:** amnesia, balance disorder, depressed level of consciousness, hypotonia, lethargy, nervous system disorder; **Psychiatric disorders:** confusional state, nervousness; **Reproductive system and breast disorders:** menorrhagia; **Skin and subcutaneous tissue disorders:** pruritus, dermatitis, dermatitis contact, erythema, periorbital oedema, skin exfoliation, toxic epidermal necrolysis

DRUG INTERACTIONS

Overview

Specific drug interaction studies were not conducted with AZARGA™ (brinzolamide/timolol) ophthalmic suspension. In clinical studies, AZARGA™ suspension was used concomitantly with the following systemic medications without evidence of adverse interactions: antihistamines, antiinfectives, cardiovascular medications, central nervous system medications, analgesic /antipyretic medications, non-steroidal anti-inflammatory drugs, psychotherapeutic agents, antidiabetic medications, and thyroid agents. However, the potential for interactions with any drug should be considered.

Drug-Drug Interactions

AZARGA™ suspension contains brinzolamide, 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 AZARGA™ suspension.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, 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. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic solutions with beta blockers such as timolol are administered concomitantly with oral calcium channel blockers, guanethidine other beta adrenergic blocking agents, antiarrhythmics, digitalis glycosides or parasympathomimetics.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta adrenergic blocking agents.

Potentiated systemic beta-blockade (e.g. decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, cimetidine) and timolol.

Drug-Food Interactions

Interactions with food are not anticipated following topical ocular administration.

Drug-Herb Interactions

Interactions with herbal products are not anticipated following topical ocular administration.

Drug-Laboratory Interactions

Interactions with laboratory tests are not anticipated following topical ocular administration.

DOSAGE AND ADMINISTRATION

Dosing Considerations

When substituting another ophthalmic antiglaucoma agent with AZARGA™ (brinzolamide/timolol) ophthalmic suspension, the other agent should be discontinued and AZARGA™ suspension should be started the following day.

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

Recommended Dose and Dosage Adjustment

The adult dose is one drop of AZARGA™ suspension in the conjunctival sac of the affected eye(s) twice daily.

Missed Dose

If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. Do not use a double dose to make up for the one missed.

Administration

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 adverse reactions.

Instruct patients to shake the bottle well before use.

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

OVERDOSAGE

For management of suspected drug overdose, consult your regional poison control centre.

No data are available in humans with regards to overdose by accidental or deliberate ingestion of AZARGA™ (brinzolamide/timolol) ophthalmic suspension.

If overdose with AZARGA™ suspension occurs, treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AZARGA™ (brinzolamide/timolol) ophthalmic suspension contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated IOP primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. The combined effect of these two agents results in additional IOP reduction compared to either compound alone.

Brinzolamide is a potent inhibitor of human CA-II, the predominant isozyme in the eye. 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.

Timolol is a non-selective beta adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Pharmacodynamics

AZARGA™ suspension, when applied topically to the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The Advanced Glaucoma Intervention Study (AGIS) (1) established elevated intraocular pressure as a positive risk factor for glaucomatous visual field loss. Eyes with intraocular pressures below 18 mmHg at all visits were found to have little to no visual field loss during the six-year monitoring period.

Clinical effects:

In a twelve-month, controlled clinical trial in patients with open-angle glaucoma or ocular hypertension who, in the investigator's opinion could benefit from a combination therapy, and

who had baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of AZARGA™ suspension dosed twice daily was 7 to 9 mmHg (2).

In a six-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of AZARGA™ suspension dosed twice daily was 7 to 9 mmHg, and was up to 3 mmHg greater than that of brinzolamide 1.0% dosed twice daily and up to 2 mmHg greater than that of timolol 0.5% dosed twice daily. A statistically superior reduction in mean IOP was observed compared to both brinzolamide and timolol at all time-points and visits throughout the study (3).

In two controlled clinical trials, the ocular discomfort upon instillation of AZARGA™ suspension was significantly lower than that of COSOPT (2, 4).

Pharmacokinetics

Table 2: Steady State Red Blood Cell Concentrations of brinzolamide and N-desethyl brinzolamide following administration of AZARGA™ Suspension in Healthy Subjects

	C₁₀₇ (μM)	AUC_{15-107day} (μM·day)
brinzolamide	18.4 ± 3.01	1681 ± 225
N-desethyl-brinzolamide	1.57 ± 1.13	118 ± 61.8

Table 3: Steady State Plasma Concentrations of timolol following administration of AZARGA™ Suspension in Healthy Subjects

	C_{max} (ng/ml)	T_{max} (h)	AUC₀₋₁₂ (ng·h/ml)	t_½ (h)
timolol	0.824 ± 0.453	0.79 ± 0.45	4.71 ± 2.49	4.8 ± 1.8 h

Absorption:

Following topical ocular administration of AZARGA™ suspension, brinzolamide and timolol are absorbed through the cornea and into the systemic circulation. In a pharmacokinetic study, healthy subjects received oral brinzolamide (1 mg) twice daily for 2 weeks to shorten the time to reach steady-state prior to the start of administering AZARGA™ suspension. Following twice daily dosing of AZARGA™ suspension in both eyes for 13 weeks, red blood cell (RBC) concentrations of brinzolamide averaged 18.8 ± 3.29 μM, 18.1 ± 2.68 μM and 18.4 ± 3.01 μM at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained (RBC saturation of CA-II at approximately 20 μM). The mean steady-state timolol plasma C_{max} was 0.824 ng/ml and T_{max} was 0.79 hours after dosing with AZARGA™ suspension.

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.

Timolol can be measured in human aqueous humour after administration of timolol ophthalmic solution and in plasma for up to 12 hours after administration of AZARGA™ suspension.

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.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. Timolol metabolism is mediated primarily by CYP2D6.

Excretion:

Brinzolamide is eliminated primarily by renal excretion (approximately 60%). About 20% of the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethyl-brinzolamide are the predominant components in the urine along with trace levels (<1%) of the N-desmethoxypropyl and O-desmethyl metabolites.

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4.8 hours after administration of AZARGA™ suspension.

Special Populations and Conditions

Pediatrics: AZARGA™ suspension has not been evaluated in the pediatric population.

Geriatrics: No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Gender: Following topical ocular administration of AZARGA™ suspension, there were no clinically relevant differences in systemic exposure to brinzolamide, N-desethyl brinzolamide or timolol, when analyzed by gender.

Race: No efficacy and safety differences due to ethnicity are expected with AZARGA™ suspension.

Hepatic Insufficiency: AZARGA™ suspension has not been studied in patients with hepatic

disease.

Renal Insufficiency: AZARGA™ suspension has not been studied in patients with renal impairment.

STORAGE AND STABILITY

Store at 2°C – 30°C. Discard 60 days after opening.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AZARGA™ (brinzolamide/timolol maleate) ophthalmic suspension contains the active ingredients brinzolamide 1.0% (10 mg/mL) and timolol 0.5% (5 mg/mL, as timolol maleate), the preservative benzalkonium chloride 0.01%, and the inactive ingredients mannitol, carbomer 974P, sodium chloride, tyloxapol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

AZARGA™ suspension is formulated at a pH of approximately 7.2 and is isotonic.

AZARGA™ suspension is supplied in an 8 mL round low density polyethylene bottle with a low density polyethylene dispensing plug and white polypropylene cap. Tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening.

Net contents are 5 mL supplied in an 8 mL bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

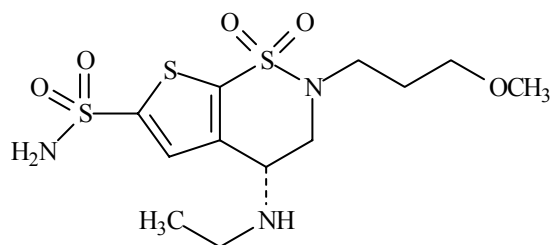
Drug Substance

Proper name: brinzolamide

Chemical name: (*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide

Molecular formula and molecular mass: C₁₂H₂₁N₃O₅S₃; 383.51

Structural formula:



Physicochemical properties: White to off-white powder or crystals. Insoluble in water; slightly soluble in alcohol and in methanol.

Drug Substance

Proper name: timolol maleate

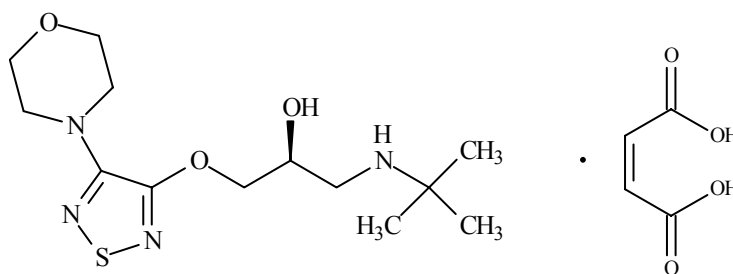
Chemical name: (-)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt)

Molecular formula: C₁₃H₂₄N₄O₃S • C₄H₄O₄

Molecular mass timolol maleate: 432.49

Molecular mass timolol: 316.42

Structural formula:



Physicochemical properties: White or almost white, odorless, crystalline powder. Soluble in water, in alcohol, and in methanol; sparingly soluble in chloroform and in propylene glycol; insoluble in ether and in cyclohexane.

CLINICAL TRIALS

Study demographics and trial design

A summary of the patient demographics for each of the 4 studies relevant to the evaluation of the efficacy and comfort of AZARGA™ (brinzolamide/timolol) ophthalmic suspension is provided in Table 4. Overall, these demographics are representative of the population that would be expected to receive this medicinal product.

Table 4: Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Intent to Treat study subjects (n=number)	Mean age (Range)	Gender
C-97-22 Safety and Efficacy	Double-masked, parallel group, randomised	AZARGA: 1 drop BID Timolol: 1 drop BID 2 weeks	n = 66	60.8 yrs (31-87 yrs)	19 M 47 F
C-05-24 Safety and Efficacy	Double-masked, parallel group, randomised	AZARGA: 1 drop BID AZOPT: 1 drop BID Timolol: 1 drop BID 6 months	n = 517	62.8 yrs (26-90 yrs)	221 M 296 F
C-05-10 Safety and Efficacy	Double-masked, parallel group, randomised	AZARGA: 1 drop BID COSOPT: 1 drop BID 12 months	n = 431	64.9 yrs (22-90 yrs)	180 M 251 F
C-05-49 Comfort	Double-masked, crossover, randomised	AZARGA: 1 drop BID COSOPT: 1 drop BID 1 week	n = 95	67.6 yrs (32-90 yrs)	33 M 62 F

Study results

Three clinical studies were conducted to assess the efficacy and safety of AZARGA™ suspension. All three studies demonstrated that AZARGA™ suspension dosed twice daily produces statistically significant and clinically relevant reductions in IOP from baseline.

An additional clinical study was conducted to evaluate the comfort of the combination product.

Comparison to Monotherapy (C-97-22)

A fourteen-day, multicentre, triple-masked, parallel group study (n=66) was conducted to evaluate AZARGA™ suspension b.i.d. compared to 0.5% timolol b.i.d. in patients with elevated IOP \geq 22 mmHg, inadequately controlled after 3 weeks of 0.5% timolol b.i.d. monotherapy.

AZARGA™ suspension dosed twice daily produced statistically significant additional mean reductions in IOP (2.8 mmHg to 3.3 mmHg) from an open-label Timolol 0.5% Solution baseline greater than 21 mmHg. Differences in mean IOP change from baseline ranged from 1.0 to 1.6 mmHg in favour of the AZARGA™ suspension treatment group and were statistically significant ($p \leq 0.0413$) for 4 of the 5 on-therapy time points.

Table 5: Mean IOP Change from Baseline (mmHg) (C-97-22)

	Baseline		Day 1	Day 7		Day 14	
	8AM	10AM	8AM	8AM	10AM	8AM	10AM
AZARGA							
Mean	24.6	23.7	-2.8	-2.7	-3.3	-3.2	-3.3
N	33	33	33	33	33	33	33
P-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Timolol							
Mean	23.9	23.4	-1.6	-1.4	-2.3	-1.7	-2.3
N	30	30	30	28	28	30	30
P-value	<.0001	<.0001	<.0001	0.0005	<.0001	<.0001	<.0001
Difference	0.7	0.3	-1.2	-1.3	-1.0	-1.6	-1.1
P-value	0.1736	0.5965	0.0200	0.0144	0.0679	0.0034	0.0413

Contribution of Elements (C-05-24)

A 6-month, multi-centre, double-masked, active-controlled, randomized, parallel group study was designed to demonstrate the contribution of elements of AZARGA™ suspension relative to its individual components, AZOPT® (brinzolamide 1.0%) suspension and Timolol 0.5% Solution, in patients with open-angle glaucoma or ocular hypertension.

AZARGA™ suspension dosed twice daily produced IOP-lowering efficacy that was superior to both AZOPT® suspension and Timolol 0.5% Solution as evidenced by statistically significantly lower ($p < 0.05$) mean IOP values at all 6 on-therapy assessment times over the 6 month study. Mean IOP in the intent-to-treat (ITT) analysis ranged from 17.1 to 19.0 mmHg for the AZARGA group, 20.4 to 22.0 mmHg for the AZOPT group, and 18.8 to 20.4 mmHg for the Timolol 0.5% Solution group. Differences in mean IOP favored the AZARGA group and ranged from -3.3 to -2.7 mmHg for comparisons against the AZOPT group, and from -1.8 to -1.3 mmHg for comparisons against the Timolol 0.5% Solution group.

AZARGA™ suspension dosed twice daily produced statistically significant and clinically relevant diurnal IOP control. Among patients enrolled at selected sites (approximately 33% of total patients in study) where additional IOP measurements were performed at 12:00 PM, 4:00 PM and 8:00 PM, AZARGA™ suspension demonstrated statistically significantly superior IOP-

lowering efficacy relative to AZOPT® suspension and Timolol 0.5% Solution. Mean IOP across these 6 additional on-therapy assessment times ranged from 17.0 to 17.8 mmHg for the AZARGA group, 20.0 to 20.8 mmHg for the AZOPT group, and 19.2 to 20.3 mmHg for the Timolol 0.5% Solution group. Differences in mean IOP between the AZARGA and AZOPT groups ranged from -3.1 to -2.2 mmHg and were statistically significant ($p < 0.05$) at each of the 6 additional on-therapy assessment times. Differences in mean IOP between the AZARGA and Timolol 0.5% Solution groups ranged from -2.8 to -1.5 mmHg and were statistically significant ($p < 0.05$) at each of the 6 additional on-therapy assessment times.

Table 6: Mean IOP Change from Baseline (mmHg) (C-05-24)

	Baseline		Combined		Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
AZARGA										
Mean	27.1	25.8	-8.3	-8.5	-8.4	-8.7	-8.3	-8.7	-8.1	-8.0
N	171	171	171	171	170	170	171	171	171	171
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
AZOPT										
Mean	27.1	25.6	-5.3	-5.2	-5.1	-5.2	-5.6	-5.3	-5.2	-5.1
N	173	173	173	173	172	172	173	173	173	173
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Timolol										
Mean	27.0	25.4	-6.8	-6.2	-6.9	-6.6	-6.9	-6.4	-6.6	-5.7
N	173	173	173	173	173	173	173	173	173	173
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

Combined = Results pooled across Week 2, Month 3 and Month 6.

Comparative Study (C-05-10)

A twelve-month, multinational study conducted at 45 centres was designed to compare the IOP-lowering efficacy and safety of AZARGA™ suspension to that of COSOPT (dorzolamide 20 mg/ml and timolol 5 mg/ml). Both medications were dosed twice daily at 8 AM and 8 PM.

AZARGA™ suspension produced statistically significant and clinically relevant reductions from baseline in IOP, with mean reductions in the per protocol analysis ranging from approximately 7 to 9 mmHg. These equate to IOP reductions of 28% to 35%. Furthermore, AZARGA™ suspension provided clinically relevant control of IOP throughout the day, with approximately 60% of patients achieving IOP levels <18 mmHg at least at 1 visit.

AZARGA™ suspension demonstrated the same IOP-lowering efficacy as COSOPT. Treatment group differences in means numerically favoured AZARGA™ suspension at 9 of 12 study visit and times in the per protocol analysis and at 11 of 12 study visits and times in the intent-to-treat analysis.

Table 7: Comparison of Mean IOP (mmHg) AZARGA versus COSOPT (C-05-10)

Timepoints		AZARGA		COSOPT		Treatment Effect		
		Mean	N	Mean	N	Difference*	Upper 95% CI	Lower 95% CI
Baseline ^a	8AM	27.3	218	27.3	201	-0.0	0.6	-0.7
	10AM	25.9	218	26.1	201	-0.2	0.4	-0.8
	4PM	24.8	218	24.8	201	-0.0	0.6	-0.6

Week 2	8AM	-8.5	216	-8.0	198	-0.6	0.2	-1.3
	10AM	-8.8	195	-8.7	185	-0.4	0.4	-1.1
Month 3	8AM	-9.1	208	-8.7	187	-0.6	0.2	-1.3
	10AM	-9.2	207	-8.8	186	-0.6	0.2	-1.3
Month 6	8AM	-8.8	205	-8.3	181	-0.5	0.3	-1.2
	10AM	-8.8	204	-8.7	181	-0.1	0.6	-0.8
	4PM	-7.5	200	-7.4	180	0.1	0.9	-0.6
Month 9	8AM	-8.7	198	-8.2	173	-0.5	0.3	-1.2
	10AM	-8.8	198	-8.6	173	-0.3	0.5	-1.1
Month 12	8AM	-8.7	191	-8.5	169	-0.1	0.6	-0.8
	10AM	-8.6	192	-8.9	168	0.2	1.0	-0.5
	4PM	-7.2	192	-7.7	168	0.7	1.4	-0.1

* negative values favour AZARGA
CI = confidence interval

Comfort Study (C-05-49)

A one-week, double-masked, randomized, active-controlled, parallel trial was conducted to evaluate the ocular discomfort of AZARGA™ suspension compared to COSOPT. Patient assessment was based on burning and stinging using a 5-point scale (0 = none, 4 = very severe).

The ocular comfort of AZARGA™ suspension was superior to COSOPT, as evidenced by a significantly higher percentage of patients on AZARGA™ suspension that experienced no burning or stinging after 1 week of dosing compared to COSOPT (48.9% and 14.9%, respectively, $p=0.0004$). The mean discomfort scores at the Week 1 visit were 1.53 for the COSOPT group and 0.77 for the AZARGA™ suspension group in the intent-to-treat analysis ($p=0.0003$).

The ocular comfort of AZARGA™ suspension was further supported by a review of treatment-related adverse events which demonstrated a higher incidence of ocular pain (23.4% vs. 10.4%) and ocular irritation (17.0% vs. 8.3%) in patients treated with COSOPT.

DETAILED PHARMACOLOGY

Brinzolamide is a carbonic anhydrase inhibitor (CAI) with high affinity for, and potent inhibitory activity against, human carbonic anhydrase II with a K_i of 0.13 nM and an IC_{50} of 3.2 nM. Carbonic anhydrase is an enzyme found in many tissues of the body, including the eye. It catalyzes 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 of sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Timolol has been utilised as the primary therapy for the reduction of elevated IOP in patients with ocular hypertension or open-angle glaucoma for many years. Tonography and fluorophotometry studies suggest that timolol's predominant action is related to a reduction in aqueous humour formation following blockade of the beta-adrenoreceptors on the non-pigmented epithelial cells of the ciliary body.

Human Pharmacodynamics

The active components of AZARGA™ suspension, brinzolamide and timolol maleate, are approved therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension, with different mechanisms of action. AZARGA™ suspension produces greater mean IOP reductions than those produced by either AZOPT® (brinzolamide 1%) ophthalmic suspension, or Timolol Maleate Ophthalmic Solution, 0.5% used alone.

Animal Pharmacodynamics

No non-clinical ocular or systemic pharmacodynamic studies were conducted on AZARGA™ suspension since the pharmacology of each active component has been well established previously in the medical and scientific literature. Previous studies have shown that the concomitant application of carbonic anhydrase inhibitors with timolol results in an additional reduction in IOP compared to the administration of either single agent (5, 6).

Human Pharmacokinetics

In Vitro Studies

No *in vitro* studies were conducted with AZARGA™ suspension in humans.

In Vivo Studies

Following twice daily topical ocular administration of AZARGA™ suspension in healthy subjects for 13 weeks (which followed a 2-week oral phase with brinzolamide 1-mg dosed twice daily, to shorten the time to reach steady-state), the mean whole blood concentrations (RBC) of brinzolamide averaged $18.8 \pm 3.29 \mu\text{M}$, $18.1 \pm 2.68 \mu\text{M}$ and $18.4 \pm 3.01 \mu\text{M}$ on Study Weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained (RBC saturation of CA-II at $\sim 20 \mu\text{M}$). The mean RBC concentrations of the active metabolite of brinzolamide (N-desethyl brinzolamide) increased gradually during the study, reaching a mean RBC concentration of $1.57 \pm 1.13 \mu\text{M}$ at Week 15. The mean $\text{AUC}_{15-107\text{day}}$ for brinzolamide and N-desethyl brinzolamide were $1681 \pm 225 \mu\text{M}\cdot\text{day}$ and $118 \pm 61.8 \mu\text{M}\cdot\text{day}$, respectively.

Following AZARGA™ suspension administration, the mean peak concentration (C_{max}) of timolol at steady-state ($0.824 \pm 0.453 \text{ ng/mL}$) was reached at an average of 0.79 ± 0.45 hours after dosing. After the peak, plasma concentrations of timolol declined with a mean $t_{1/2}$ of 4.8 ± 1.8 hours. The mean steady-state C_{max} of timolol following bilateral BID topical ocular administration of AZARGA™ suspension is over 100 times lower than the mean C_{max} ($84.3 \pm 44.8 \text{ ng/mL}$) observed in subjects following a 20-mg oral dose of Timolol.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single Dose Studies

Brinzolamide/Timolol Combination

Single-dose studies were not conducted with the brinzolamide/timolol combination. However, single dose topical ocular and oral studies were conducted with brinzolamide and single dose toxicity studies by three routes of administration were conducted with timolol.

Brinzolamide

Single-dose toxicity studies included a 1-day topical ocular irritation evaluation in rabbits and acute oral toxicity studies in rats and mice. Exaggerated topical ocular dosing studies with a 2.0% formulation of brinzolamide indicated that ocular irritation and comfort scores were consistent with those normally observed with ophthalmic suspensions, and no significant clinical findings were noted.

Single-dose oral toxicity studies were conducted in rats and mice to assess the acute toxicity of brinzolamide. The oral LD₅₀ of brinzolamide in mice was estimated to be 1,400 mg/kg, with the oral LD₅₀ in rats estimated at 1,000 to 2,000 mg/kg.

Timolol

Acute oral dosing studies established an LD₅₀ of approximately 1000 mg/kg for mice and rats. The most frequent clinical observations were decreased activity and bradypnea. Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Repeat-Dose Topical Ocular Administration

Brinzolamide/Timolol Combination

Toxicologic evaluations of the brinzolamide/timolol fixed combination conducted during 6 and 9 month evaluations in New Zealand albino and pigmented rabbits revealed no significant treatment-related observations during in-life or after microscopic evaluation of ocular and systemic tissues. The only finding that has been observed consistently in topical ocular rabbit studies with brinzolamide has been slight corneal thickening. This has been established as a species-specific effect and has not been observed in monkey topical ocular studies with brinzolamide or clinical studies with AZARGA™ (brinzolamide/timolol) ophthalmic suspension. In addition, microscopic evaluation of the corneal tissue in animals where thickening has occurred did not reveal any adverse cellular effects.

Table 8: Summary of Repeated Dose Topical Ocular Nonclinical Safety Studies Conducted with A Combination of Brinzolamide and Timolol

Duration / Species / Strain	No. of Animals	Dose and Frequency	Brinzolamide/ Timolol Doses (mg/ml)	Results/Findings
2-Week/ Rabbit/ NZW	4/sex/group	1 drop BID, OU	UC, 0/0 (Vehicle), <u>20/5</u>	Slight increase in corneal thickness in treated groups
3/6-Month/ Rabbit/ NZW	10(4 ^a)/sex/group	1 drop TID, OU	UC, 0/0 (Vehicle), 10/5, <u>20/5</u>	Slight increase in corneal thickness in treated groups
9-Month/ Rabbit/ NZ Pigmented	6/sex/group	1 drop BID or TID, OU	UC, 0/0 ^c (Vehicle) ^c , 10/5 ^b , <u>20/5^c</u>	No test-article related changes
^a euthanised at 3 months ^b one group was dosed BID and a second group was dosed TID ^c dosed TID UC = untreated control; BID = twice a day; TID = three times a day; OU = both eyes The highest No Observed Adverse Effect Level (NOAEL) is underlined.				

Brinzolamide

Five repeat-dose topical ocular studies were conducted in rabbits, ranging in duration from 1 to 6 months, and a 1-year topical ocular study was conducted in nonhuman primates.

These studies demonstrated that there was no significant ocular toxicity or irritation when the drug was administered topically. Irritation scores were unremarkable and similar to controls.

Concentrations of brinzolamide ophthalmic suspension as high as 4.0% were administered chronically up to 4 times a day in rabbits and three times a day in monkeys without significant toxicological findings.

Table 9: Summary of Repeated-Dose Topical Ocular Nonclinical Safety Studies Conducted with Brinzolamide

Duration / Species / Strain	No. of Animals	Dose and Frequency	Brinzolamide Doses (mg/ml)	Results
1-Month/ Rabbit/NZW	4/sex/group	2 drops TID; OD	UC, 0 (Vehicle), 10, <u>30</u> - gel forming solution	No significant findings
1-Month/ Rabbit/ NZW	4/sex/group	1 drop QID; OD	UC, 0 (Vehicle), 20, <u>40</u> - suspension	No significant findings
1/3-Month/ Rabbit/ NZW	1-Month 3/sex/group; 3-Month 4/sex/group	2 drops QID; OD	UC, 0 (Vehicle), 20, <u>40</u> - suspension	No significant findings
3-Month/ Rabbit/ NZW	5/sex/group	1 drop TID; OU	UC, 0 (Vehicle), 10, <u>20</u> - suspension	Slight increase in corneal thickness in brinzolamide treated groups
6-Month/ Rabbit/ NZW	10/sex/group	2 drops QID; OD	UC, 0 (Vehicle), 20, <u>40</u> - suspension	No significant findings
1-Year/ Monkey/ Cynomolgus	4/sex/group	2 drops TID; OD	UC, 0 (Vehicle), 10, 20, <u>40</u> - suspension	No significant findings
Underlined = NOAEL - the identified (No Adverse Effect Level) for the study. UC = untreated control; TID = three times a day; QID = four times a day; NZW = New Zealand White; OD = right eye; OU = both eyes				

Timolol

No adverse ocular effects were observed in rabbits and dogs administered Timolol 0.5% Solution

topically in studies lasting one and two years, respectively.

Repeat-Dose Systemic Administration

Brinzolamide/Timolol Combination

Systemically administered repeat-dose studies were not conducted with the brinzolamide/timolol combination. Repeat-dose oral toxicity studies were conducted with brinzolamide and with timolol.

Brinzolamide

Repeat-dose oral toxicity studies in rats and mice established the urinary system as the primary site of toxicity, consistent with known effects of CAIs. Pharmacological effects on urine volume, specific gravity and electrolytes were observed. Minimal to mild nephropathy, with crystalline material in the urine, was observed at the higher dose levels. The No Observed Effect Level (NOEL) for brinzolamide in a chronic 6-month rat study was 1 mg/kg/day with a steady-state whole blood concentration of 62.7 to 70.8 μ M.

Timolol

Timolol was administered orally to rats at dose levels 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

In a 54 week oral study, timolol was administered to dogs at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

In rats treated with 100 to 400 mg/kg timolol maleate for seven weeks, excessive salivation seen 5 to 10 minutes after dosing had a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptyalism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg timolol maleate or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15 day intravenous toxicity study.

Genotoxicity:

Brinzolamide

Two *in vitro* and two *in vivo* mutation assays were conducted with brinzolamide in order to evaluate the genotoxicity potential of the drug substance. Results of the *in vitro* bacterial mutation and the two *in vivo* assays unequivocally demonstrate a lack of mutagenicity. The *in*

in vitro mammalian cell mutation assay indicated a potential for mutagenicity, but when the cytotoxicity and class of drug was put into context, brinzolamide was considered nonmutagenic.

Timolol

In the Ames assays, the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, and the ratio of test to control revertants did not reach the criterion for a positive Ames test. Timolol maleate was not mutagenic in the *in vitro* neoplastic cell transformation assay (up to 100 µg/ml). Timolol maleate was also not mutagenic when tested *in vivo* in the mouse micronucleus test and cytogenetic assay (doses up to 800 mg/kg). (7)

Carcinogenicity:

Brinzolamide

An initial cell proliferation study in rats confirmed an absence of proliferation potential with brinzolamide. Brinzolamide has been characterised as unequivocally noncarcinogenic based on 2-year oral dosing studies in mice and rats.

Timolol

Two-year oral carcinogenicity studies were conducted in the mouse and the rat with timolol. In the mouse study, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 35,000 times the systemic exposure following the maximum recommended human ophthalmic dose of 5 mg/ml), but not at 5 or 50 mg/kg/day (approximately 350 or 3,500, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). Subsequently, this increase was determined to be associated with elevated serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. The relevance of this finding in mice has not been established in humans (7).

In the rat study, where timolol maleate was administered orally, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered 100 mg/kg/day oral doses equivalent to approximately 7,000 times the maximum recommended human ophthalmic dose (7).

Reproduction and Development:

Brinzolamide

Brinzolamide when given orally demonstrated no effect on male or female fertility.

Brinzolamide increased the incidence of unossified sternebrae or hyoid and reduced ossification of the skull in rats at 18 mg/kg/day given orally. Reduced ossification was not dose-dependent. In rabbits, no malformations were observed and ossification appeared to be unaffected. In a peri- and postnatal effect study, F₁ pup body weights were significantly reduced, as compared with

controls, throughout the lactation period, at the 15 mg/kg/day dose level. These effects are comparable with other drugs of this class (8, 9, 10).

Timolol

In reproduction and fertility studies in rats with timolol, there were no adverse effects on male or female fertility at doses up to 150 mg/kg/day or 10,000 times the systemic exposure following the maximum recommended human ophthalmic dose (7).

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (3,500 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of foetal malformations. Although delayed foetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (71,000 times the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of foetal resorptions. Increased foetal resorptions were also seen in rabbits at doses of 90 mg/kg/day or 6,400 times the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity (7).

Other Studies:

Brinzolamide

Brinzolamide is considered to have little or no potential to induce contact sensitisation based on a guinea pig maximisation test. The main impurities, S-isomer and N-desethyl were characterised as nongenotoxic in bacterial mutagenicity and mouse micronucleus tests. In addition, a 1-month topical ocular rabbit study was performed with concentrations of S-isomer up to 2 mg/ml. This study determined that the impurity S-isomer was safe in the AZOPT® formulation well above the specified limit.

Timolol

The potential for delayed contact sensitisation of timolol maleate was evaluated in the guinea pig maximisation test. No significant response occurred after the primary challenge, and a re-challenge was conducted on Day 35. Responses in both the primary (0/20) and re-challenge (1/20) procedures were comparable with negative controls (0/10). In this study, timolol maleate showed no evidence of delayed contact dermal sensitisation.

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PART III: CONSUMER INFORMATION

Pr **AZARGA™**
brinzolamide 1.0% / timolol 0.5%
ophthalmic suspension

This leaflet is part III of a three-part "Product Monograph" published when AZARGA™ suspension was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AZARGA™ suspension. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

AZARGA™ suspension is used to treat high pressure in the eye. This pressure can lead to an illness called glaucoma.

What it does:

AZARGA™ suspension is a combination of treatments to reduce pressure in the eye for conditions such as glaucoma. It contains two ingredients which work together to reduce pressure within the eye. Brinzolamide is a carbonic anhydrase inhibitor and timolol is a beta-blocker. Both brinzolamide and timolol work by reducing the production of fluid within the eye.

When it should not be used:

- if you are allergic to any of the ingredients of AZARGA™ suspension, other beta-blockers or sulfonamides. For a full list of ingredients please see below
- if you have respiratory problems such as asthma, bronchitis, severe chronic obstructive pulmonary disease (COPD) or other types of breathing problems
- if you have a slow heart beat, heart failure or disorders of heart rhythm
- if you have too much acidity in your blood (a condition called hyperchloraemic acidosis)
- if you have kidney problems

What the medicinal ingredients are:

The active ingredients are brinzolamide and timolol maleate. One ml of suspension contains 10 mg of brinzolamide and 5 mg of timolol (as timolol maleate).

What the important nonmedicinal ingredients are:

Preservative: benzalkonium chloride. The other ingredients are carbomer 974P, disodium edetate, mannitol, purified water, sodium chloride and tyloxapol. Tiny amounts of hydrochloric acid and/or sodium hydroxide are added to keep acidity levels (pH levels) normal.

What dosage forms it comes in:

AZARGA™ suspension contains tiny white particles suspended in a clear liquid. It is supplied as 5 mL of suspension in an 8 mL plastic DROP-TAINER® dispenser bottle with a screw cap.

WARNINGS AND PRECAUTIONS

BEFORE you use AZARGA™ suspension, talk to your doctor or pharmacist if you have:

- **angina (chest pains), circulation problems or low blood pressure.** AZARGA™ suspension may make any of these worse.
- **diabetes.** AZARGA™ suspension can mask the symptoms of low blood sugar (hypoglycaemia) such as shakiness and dizziness, so you need to use it with care.
- **liver problems**
- **thyroid problems**
- **dry eyes or cornea problems**

While you are using AZARGA™ suspension, consult your doctor immediately if:

- you develop an eye infection, swelling, redness or irritation of the eyelid
- you suffer any eye injury or have eye surgery

Pregnancy or breast-feeding

If you are pregnant, or might get pregnant, talk to your doctor before you use AZARGA™ suspension. If you are breast-feeding, you can use AZARGA™ suspension.

Driving and using machines

You may find that your vision is blurred for a time just after you use AZARGA™ suspension. Do not drive or use machines until your vision is clear.

If you wear contact lenses

There is a preservative in AZARGA™ suspension (benzalkonium chloride) that can discolour soft contact lenses and may cause eye irritation. Therefore, do not wear contact lenses while using AZARGA™ suspension. Wait 15 minutes after using AZARGA™ suspension before putting your lenses back in.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all drugs, including eye drops, that you are using or plan to use, including those without a prescription. Drugs that may interact with AZARGA™ suspension include heart or blood pressure medications such as beta-blockers, calcium channel blockers, quinidine, digitalis, guanethidine and other beta-adrenergic blocking agents, and cimetidine.

PROPER USE OF THIS MEDICATION

Always use AZARGA™ suspension exactly as your doctor has told you.

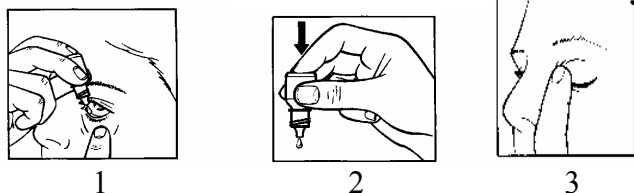
Usual adult dose:

One drop in the eye or eyes, twice a day - morning and night.

Only use AZARGA™ suspension in both eyes if your doctor told

you to. Take it for as long as your doctor told you to.

How to Use:



- Get the AZARGA™ suspension bottle and a mirror.
- Wash your hands.
- Shake well before use.
- Twist off the bottle cap.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a ‘pocket’ between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops.
- Gently press on the base of the bottle to release one drop of AZARGA™ suspension at a time
- Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).
- After using AZARGA™ suspension, press a finger into the corner of your eye, by the nose (picture 3). This helps to stop AZARGA™ suspension getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Use up one bottle before opening the next bottle.

If a drop misses your eye, try again.

If you are using other eye drops, wait at least 5 minutes between using AZARGA™ suspension and the other drops.

Overdose:

If you use more AZARGA™ suspension than you should, rinse your eye with warm water. Do not put in any more drops until it is time for your next regular dose.

In case of overdose, particularly oral ingestion, contact your doctor, hospital emergency department, or regional poison control centre.

Missed Dose:

If you forget to use AZARGA™ suspension, continue with the next dose as planned. Do not use a double dose to make up for the missed dose. Do not use more than one drop in the affected eye(s) twice daily.

If you stop using AZARGA™ suspension without speaking to

your doctor, the pressure in your eye will not be controlled which could lead to a loss of sight.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AZARGA™ suspension can cause side effects although not everybody gets them.

You can usually carry on taking the drops, unless the effects are serious. If you are worried, talk to your doctor or pharmacist.

If you get any severe allergic reaction while you are using AZARGA™ suspension, contact your doctor immediately.

The most common side effects in the eye include blurred vision, eye irritation, eye pain, and abnormal eye sensation.

Less common side effects in the eye include redness of the eye, decreased pressure in eye, itchy eye, eye surface inflammation with surface damage, dry eye, eye discharge, allergic conjunctivitis (eye allergy), corneal disorder, eyelid abnormality, irritation, itching, redness, pain, swelling, or crusting, increased tear production, inflammation inside the eye, sensitivity to light, and tired eyes.

The most common side effect in other areas of body includes bad taste.

Less common side effects in other areas of body include decreased blood pressure, chronic lung disease, cough, difficulty sleeping, hair disorder, runny nose, skin inflammation, redness, or itching, and throat irritation.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	slow heartbeat			✓
Rare	Heart effects such as irregular heartbeat, low blood pressure			✓
	Allergic reactions with symptoms such as swelling of the mouth and throat, shortness of breath, hives, severe itching and rash			✓

This is not a complete list of side effects. For any unexpected effects while taking AZARGA™ suspension, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use AZARGA™ suspension after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

Store at 2°C to 30°C. Discard 60 days after opening.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- report online at www.healthcanada.gc.ca/medeffect
- call toll-free at 1-866-234-2345
- complete a Canada Vigilance Reporting Form and:
 - fax toll-free to 1-866-678-6789
 - mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found on the Health Canada website or by contacting the sponsor, Alcon Canada Inc., at: 1-800-613-2245

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