AUSTRALIAN PRODUCT INFORMATION – AZARGA (BRINZOLAMIDE AND TIMOLOL MALEATE) EYE DROPS

1 NAME OF THE MEDICINE

Brinzolamide and timolol maleate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The eye drops suspension contains 10 mg/1 mL (1%) brinzolamide and 5 mg/1 mL (0.5%) timolol (as timolol maleate) and also 0.1 mg/1 mL benzalkonium chloride as a preservative. The pH of the eye drops suspension is approximately 7.2.

Excipient with known effect: benzoates, sulfites and hydroxybenzoates.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops.

AZARGA is a white to off-white uniform suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient IOP reduction.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage is one drop of AZARGA in the conjunctival sac of the affected eye(s) twice daily. Patient should be instructed to shake the bottle well before use.

Nasolacrimal occlusion and closing the eyelid for two minutes, after instillation are recommended. This may reduce the systemic absorption of eye drops, decrease in systemic adverse reactions and an increase in local activity.

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

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) twice daily.

When substituting another ophthalmic antiglaucoma agent with AZARGA, the other agent should be discontinued and AZARGA should be started the following day.

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. Patient should be instructed to keep the bottle tightly closed when not in use.

Patients must be instructed to remove soft contact lenses prior to application of Azarga and to wait fifteen 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.

4.3 CONTRAINDICATIONS

A history of hypersensitivity to brinzolamide and other sulphonamides, timolol, or any other component of the medication.

The following conditions may also contraindicate the use of AZARGA:

- reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- hypersensitivity to other beta-blockers.
- sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, sino-atrial block, sick sinus syndrome.
- severe allergic rhinitis and bronchial hyperreactivity
- hyperchloraemic acidosis.
- severe renal impairment (see section 4.4 Special warnings and precautions for use – Use in hepatic impairment and use in renal impairment).

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FOR TOPICAL USE ONLY - NOT FOR INJECTION OR ORAL INGESTION

AZARGA should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Systemic effects

Like other topically applied ophthalmic agents, brinzolamide and timolol are absorbed systemically. Systemic absorption can be minimised by nasolacrimal occlusion or closing the eyelids for two minutes (see Section 4.2 Dose and method of administration). This may result in a decrease in systemic side effects and an increase in local activity.

Brinzolamide

AZARGA contains brinzolamide, a sulphonamide. The same types of undesirable effects that are attributable to sulphonamides may occur with topical administration. Hypersensitivity reactions reported with sulphonamide derivatives, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving AZARGA as it is absorbed systemically. 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, discontinue use of this medicine immediately.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. AZARGA should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

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. The concomitant administration of AZARGA and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Timolol

Cardiovascular Safety

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 timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked.

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory Reactions

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.

Diabetes mellitus

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.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask the signs of hyperthyroidism.

Muscle weakness

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness).

Beta-adrenergic blocking agents may also cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

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 more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline (epinephrine) used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. Timolol, acetazemide) after filtration procedures.

Surgical anaesthesia

Beta-blocking opthalmological preparations may block systemic beta-agonist effects, e.g. of adrenaline (epinephrine). The anaesthesiologist should be informed when the patient is receiving timolol.

Ocular effects

AZARGA has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

There is limited experience with AZARGA in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be utilized in treating these patients and close monitoring of IOP is recommended.

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. The use of carbonic anhydrase inhibitors can also lead to corneal decompensation and oedema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Use with contact lenses

AZARGA 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 and wait 15 minutes after instillation of the dose before reinsertion.

Use in hepatic impairment

No studies have been conducted with AZARGA in patients with hepatic impairment. No dosage adjustment is necessary in patients with hepatic impairment

Use in renal impairment

No studies have been conducted with AZARGA in patients with renal impairment. No dosage adjustment is necessary in patients with mild to moderate renal impairment.

AZARGA has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA is therefore contraindicated in patients with severe renal impairment.

Use in the elderly

There are no modifications to the recommended dosing regimen for elderly patients.

Paediatric use

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Effects on laboratory tests

Not data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed with AZARGA.

Brinzolamide

AZARGA contains brinzolamide, a carbonic anhydrase inhibitor and, although administered topically, it's 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 AZARGA.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients treated with an oral carbonic anhydrase inhibitor and brinzolamide eye drops. The concomitant administration of eye drops containing brinzolamide and oral carbonic anhydrase inhibitors is not recommended.

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 and ritonavir 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.

Timolol

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers or beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides or parasympathomimetics. The use of two local beta-adrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended.

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

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

Beta-adrenergic blocking agents may increase the hypoglycaemic effect of antidiabetic agents. Beta-adrenergic blocking agents can mask the signs and symptoms of hypoglycaemia.

Beta blockers can decrease the response to adrenaline (epinephrine) used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section 4.4 Special warnings and precautions for use - Anaphylactic reactions)

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effects of AZARGA on male or female fertility. Studies in rats, in which animals were treated orally with brinzolamide up to 18 mg/kg/day or with timolol up to 100 mg/kg/day, showed no adverse effects on male or female fertility.

Use in pregnancy – Pregnancy Category C

No studies have been conducted with AZARGA in pregnant women, and no animal studies have been conducted with the combined components to evaluate effects on reproduction. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. AZARGA should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. However, if AZARGA is administered until delivery, the neonate should be carefully monitored during the first days of life.

Brinzolamide

Developmental toxicity studies with brinzolamide in rabbits at oral doses up to 6 mg/kg/day produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of foetal variations, e.g. accessory skull bones; at 1 and 6 mg/kg/day, the incidence was only slightly higher than seen historically. In rats, statistically significant decreased bodyweights of foetuses from dams receiving oral doses of 18 mg/kg/day during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. No treatment-related malformations were seen. Exposure levels are much lower following topical administration of brinzolamide. There are no adequate data from the use of brinzolamide in pregnant women. The potential risk for humans is unknown.

Timolol

Timolol maleate was not teratogenic in mice, rats and rabbits. Embryo-foetal development studies with timolol maleate in mice and rabbits showed no evidence of embryo-foetal toxicity at oral doses up to 50 mg/kg/day. At higher doses, increases in resorptions and foetal variations (14 ribs and hypoplastic sternebrae) in mice (1000 mg/kg/day) and increased resorption in rabbits (≥90 mg/kg/day) were observed. In rats, delayed ossification was seen at oral doses ≥50 mg/kg/day, and decreased number of caudal vertebral bodies and arches, and an increase in hypoplastic sternebrae

were noted at 500 mg/kg/day. In humans, well-controlled epidemiological studies with systemic use of beta-adrenergic blocking agents did not indicate malformative effects, but show a risk of intra uterine growth retardation. In addition, signs and symptoms of beta blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in foetuses or neonates when beta-blockers have been administered until delivery. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of the foetus/newborn child but bradycardia and arrhythmia have been reported in one case in the foetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available.

Use in lactation

It is not known whether brinzolamide is transferred into human milk following topical ocular administration. Timolol is detectable in human milk following topical ocular administration.

Studies in animals have shown that following oral administration brinzolamide is excreted in breast milk. Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. Decreases in pup bodyweights were observed at 15 mg/kg/day in a prenatal and postnatal study in which rats were given brinzolamide by oral gavage at doses up to 15 mg/kg/day.

Because of the potential for serious adverse reactions in breastfed infants from brinzolamide and timolol, a decision should be made whether to discontinue breastfeeding or to discontinue AZARGA, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

However, 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. Carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In two clinical trials of 6 and 12 months duration involving 394 patients treated with AZARGA, the most frequently reported adverse reaction was transient blurred vision upon instillation (3.6%), lasting from a few seconds to a few minutes.

The following adverse reactions were assessed to be treatment-related. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Psychiatric disorders:

Uncommon (≥0.1% to <1%): insomnia

Nervous system disorders:

Common (≥1% to <10%): dysgeusia

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic undesirable effect associated with the use of AZARGA during clinical studies. It is probably caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal. Nasolacrimal occlusion and gently closing the eyelid after instillation may help reduce the incidence of this effect.

Eye disorders:

Common (≥1% to <10%): blurred vision, eye pain, eye irritation, foreign body sensation in eyes

Uncommon (≥0.1% to <1%): corneal erosion, punctate keratitis, dry eye, eye discharge, eye pruritus, ocular hyperaemia, blepharitis, allergic conjunctivitis, corneal disorder, anterior chamber flare, conjunctival hyperaemia, eyelid margin crusting, asthenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis, erythema of eyelid, photophobia, lacrimation increased, sclera hyperaemia.

Vascular disorders:

Uncommon (≥0.1% to <1%): decreased blood pressure

Respiratory, thoracic and mediastinal disorders:

Uncommon (≥0.1% to <1%): chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough

Skin and subcutaneous tissue disorders:

Uncommon (≥0.1% to <1%): hair disorder, lichen planus

Post Marketing Experience

The following adverse reactions are classified according to the following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. These adverse reactions were obtained from clinical trials.

Table 1. Adverse reactions in clinical trials

System organ classification	Frequency	Adverse reaction
Blood and lymphatic system disorders	Uncommon (≥0.1% to <1%)	White blood cell count decreased
Psychiatric disorders	Uncommon (≥0.1% to <1%)	Insomnia
Nervous system disorders	Common (≥1% to <10%)	Dysgeusia
Eye disorders	Common (≥1% to <10%)	Punctate keratitis, blurred vision, eye pain, eye irritation
	Uncommon (≥0.1% to <1%)	Keratitis, corneal erosion, photophobia, anterior

		chamber flare, dry eye, vital dye staining cornea present, eye pruritus, foreign body sensation in eyes, lacrimation increased, eye discharge, erythema of eyelid, scleral hyperaemia, ocular hyperaemia, conjunctival hyperaemia.
	Rare (≥0.01% to <0.1%)	Eyelid margin crusting
Cardiac disorders	Common (≥1% to <10%)	Heart rate decreased
Vascular disorders	Uncommon (≥0.1% to <1%)	Blood pressure decreased
Respiratory, thoracic and mediastinal disorders	Uncommon (≥0.1% to <1%)	Cough
	Rare (≥0.01% to <0.1%)	Oropharyngeal pain, rhinorrhoea
Renal and urinary disorders	Uncommon (≥0.1% to <1%)	Blood urine present
General disorders and administration site conditions	Uncommon (≥0.1% to <1%)	Malaise

Additional adverse reactions identified from post-marketing surveillance include the following.

Frequencies cannot be estimated from the available data.

Table 2. Adverse reactions from post-marketing surveillance (frequency not known)

System organ classification	Adverse reaction
Immune system disorders	Anaphylactic shock, hypersensitivity
Cardiac disorders	Palpitations
Ear and labyrinth disorders	Tinnitus
Psychiatric disorders	Hallucination, depression
Nervous system disorders	Dizziness, paraesthesia, headache
Eye disorders	Visual impairment, eyelid oedema, , conjunctivitis, eye allergy
Vascular disorders	Blood pressure increased
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, epistaxis
Gastrointestinal disorders	Diarrhoea, dry mouth, abdominal pain upper, abdominal discomfort, nausea
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), erythema, pruritis, alopecia, rash
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Chest pain, fatigue
Investigations	Blood pressure increased

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported. A topical overdose of AZARGA may be flushed from the eye(s) with warm tap water. If an overdose with AZARGA occurs, treatment should be symptomatic and supportive. In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

Due to brinzolamide, 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

AZARGA contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated intraocular pressure (IOP) primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. Clinical data demonstrates that the combined effect of these two active substances results in additional IOP reduction compared to either compound alone.

Brinzolamide exhibits a high affinity for and is a potent inhibitor of human carbonic anhydrase II (CA-II). Carbonic anhydrase exists as a number of isoenzymes and is found in many tissues in the body; CA-II is the predominant iso-enzyme in the eye. Inhibition of CA-II 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. Brinzolamide exhibited minimal cardiovascular effects, including no inducement of QTc prolongation and no or minimal effect on blood pressure and heart rate, and had no significant local anaesthetic (membrane stabilising) activity on the cornea.

Timolol is a non-selective beta-adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or local anaesthetic (membrane-stabilising) activity. The precise mechanism of action of timolol in lowering IOP is not clearly established at this time, although tonography and fluorophotometry studies suggest that its predominant action is related to reduced aqueous humour formation; a slight increase in outflow facility was also observed in some studies.

Clinical trials

In a twelve-month, double-masked, randomised clinical trial in patients (n=437) with open-angle glaucoma or ocular hypertension who, in the investigator's opinion, could benefit from combination therapy and who had baseline mean IOP of 25 to 27 mm Hg, the mean IOP-lowering effect of AZARGA was 7 to 9 mm Hg and for dorzolamide 20 mg/mL + timolol 5mg/mL it was 7 to 9 mm Hg, when dosed twice daily. The non-inferiority of AZARGA as compared to dorzolamide 20 mg/mL + timolol 5 mg/mL in the mean IOP reduction was demonstrated across all on-therapy time-points at all visits. When evaluated at each visit, up to 60% of patients in the AZARGA group and up to 59% of patients in the dorzolamide 20 mg/mL group had IOP of less than 18 mm Hg.

In a six-month, double-masked, randomised clinical study in patients (n=523) with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mm Hg, the mean IOP-lowering effect of AZARGA dosed twice daily was 8 to 9 mm Hg, and was up to 3 mm Hg greater than that of brinzolamide 10 mg/mL dosed twice daily and up to 2 mm Hg greater than that of timolol 5 mg/mL dosed twice daily. A statistically superior reduction ($p < 0.05$) in mean IOP was observed compared to both brinzolamide and timolol at all on-therapy time-points and visits throughout the study. IOP measurements conducted at 8 am, 10 am, 12 pm, 4 pm and 8 pm confirm that diurnal IOP control is superior ($p < 0.05$) and clinically relevant for AZARGA compared to either brinzolamide 10 mg/mL or timolol 5 mg/mL. The primary efficacy endpoint of mean IOP at 8 am and 10 am post dose for this study can be seen in Table 3 below.

Table 3. Mean IOP (mm/Hg)

	Mean IOP (mmHg)							
Visit	**Baseline**		**Week 2**		**Month 3**		**Month 6**	
Time point	**8am**	**10am**	**8am**	**10am**	**8am**	**10am**	**8am**	**10am**
Azarga	27.1	25.8	18.6	17.1	18.8	17.2	19.0	17.8
Brinzolamide	27.1	25.6	22.0	20.4	21.5	20.4	21.9	20.5
Timolol	27.0	25.4	20.1	18.8	20.1	19.0	20.4	19.6

* $p<0.05$ compared to brinzolamide and timolol at all on therapy time points

In a 7-day double masked, randomised clinical trial (n=96), the ocular comfort, based on burning and stinging, of AZARGA was superior (p=0.0003) to that of dorzolamide 20 mg/mL + timolol 5 mg/mL. A comparison of the frequency distribution of the severity of ocular discomfort demonstrated a significant difference (p=0.0001) between the two treatment groups, with AZARGA having a lesser percentage of patients experiencing mild, moderate and severe ocular discomfort compared to dorzolamide 20 mg/mL + timolol 5 mg/mL. A significantly higher percentage of patients randomized to AZARGA experienced no ocular discomfort after 1 week of dosing (p=0.0004) compared to patients who received dorzolamide 20 mg/mL + timolol 5 mg/mL.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following topical ocular administration, 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 starting AZARGA administration. Following twice daily dosing of AZARGA for 13 weeks, the concentrations of brinzolamide in erythrocytes at weeks 4, 10 and 15, averaged 18.8 $\pm$ 3.29 µM, 18.1 $\pm$ 2.68 µM and 18.4 $\pm$ 3.01 µM respectively. Steady state concentrations of brinzolamide in erythrocytes may not bear a simple relationship to plasma concentrations of the drug, which have been observed to be low and generally below assay quantitation limits (<10 ng/mL) following topical ocular administration in other studies.

At steady state, following administration of AZARGA, the mean plasma C_{max} and $AUC_{0\text{-}12h}$ of timolol were 27% and 28% lower (C_{max}: 0.824 $\pm$ 0.453 ng/mL; $AUC_{0\text{-}12h}$: 4.71 $\pm$ 4.29 ng h/mL), respectively in comparison to the administration of timolol 5 mg/mL (C_{max}: 1.13 $\pm$ 0.494 ng/mL; $AUC_{0\text{-}12h}$: 6.58 $\pm$ 3.18 ng h/mL). The lower systemic exposure to timolol following AZARGA administration is not clinically relevant. Following administration of AZARGA, mean C_{max} of timolol was reached at 0.79 $\pm$ 0.45 hours.

Distribution

Plasma protein binding of brinzolamide is moderate (about 60%). Brinzolamide is sequestered in red blood cells (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 RBCs and tissue carbonic anhydrase results in low plasma concentrations.

Ocular tissue distribution data in rabbits showed that timolol can be measured in aqueous humour up to 48 hours after administration of AZARGA. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of AZARGA.

Metabolism

The metabolic pathways for brinzolamide involve N-dealkylation, 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* studies show that the metabolism of brinzolamide mainly involves CYP3A4 as well as at least four other isozymes (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 gives 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 found 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Brinzolamide did not display mutagenic potential in bacteria (Ames test) or produce chromosomal damage *in vivo* (mouse micronucleus test). Brinzolamide did induce forward mutations in the mouse lymphoma assay *in vitro* in the presence, but not in the absence, of metabolic activation. Brinzolamide was negative in a sister chromatid exchange assay in mice. Timolol was not genotoxic in assays for mutagenicity (Ames test) and clastogenicity (mouse micronucleus and cytogenic assays).

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of AZARGA.

Brinzolamide

A 2-year bioassay, in with rats were treated with brinzolamide by oral gavage at doses up to 8 mg/kg/day, revealed no evidence of a carcinogenic effect. A similar study conducted in mice, involving oral dosing at 0, 1, 3 or 10 mg/kg/day for 2 years, revealed a statistically significant increase in urinary bladder tumours in females at 10 mg/kg/day, and dose-related proliferative changes in the urinary bladder in females at all dose levels and among males at 10 mg/kg/day. The elevated bladder tumour incidence was primarily due to the increased incidence of a tumour and was considered to be unique to mice.

Timolol

No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100 mg/kg/day in rats and up to 50 mg/kg/day in mice. However, there was a statistically significant increase in the incidence of adrenal pheochomocytomas in male rats administered 300 mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas were found at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, carbomer 974P, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (for pH adjustment) purified water and benzalkonium chloride.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Discard container 4 weeks after opening.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C. Refrigerate. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

AZARGA is presented in an 8 mL round opaque low density polyethylene bottle dispenser containing 5 mL suspension.

Consumer Medicine Information is supplied with this product.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

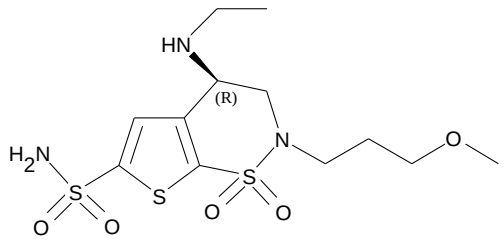
Brinzolamide is a white to off-white, crystalline powder which is very slightly soluble in water at neutral pH.

Timolol maleate is a white to off-white, crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

Chemical structure

The chemical structure of each active ingredient is represented below:

Brinzolamide

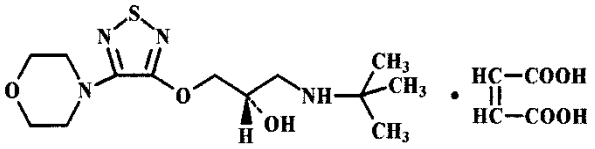


Chemical name: (R)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

Empirical formula: $C_{12}H_{21}N_3O_5S_3$

Molecular weight: 383.51

Timolol maleate



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

Empirical formula: $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$

Molecular weight: 432.50

CAS Number

Brinzolamide: 138890-62-7

Timolol maleate: 26921-17-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

5 February 2010

10 DATE OF REVISION

27 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Replace “DROP-TAINER®” with “bottle”