

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

AZARGA[®] brinzolamide 1%;10 mg/mL and timolol 0.5%; 5mg/mL eye drops.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azarga contains the active ingredients brinzolamide 1%;10 mg/mL and timolol 0.5%; 5mg/mL.

Excipients with known effects

Benzalkonium chloride 0.1 mg in 1 mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.

White to off-white uniform sterile suspension for multiple-dose ophthalmic use.

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. Shake the bottle well before use.

Nasolacrimal occlusion and gently closing the eyelid after instillation are recommended. This may reduce the systemic absorption of eye drops and result in a decrease in systemic adverse reactions.

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 anti-glaucoma agent with Azarga, the other agent should be discontinued and Azarga should be started the following day.

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.

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

4.3 Contraindications

A history of hypersensitivity to brinzolamide and other sulphonamides, timolol, or any other component of the medication (refer to section 6.1 for list of excipients).

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 4.4 Special warnings and precautions for use “Hepatic / 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. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. 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. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Use with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. If signs of serious reactions or hypersensitivity occur, discontinue use of this medicine.

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's 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 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 ophthalmological preparations may block systemic beta-agonist effects, e.g. of adrenaline. 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.

Paediatric use

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

Use in the elderly

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

Hepatic / Renal Impairment

No studies have been conducted with Azarga in patients with hepatic or renal impairment. No dosage adjustment is necessary in patients with hepatic impairment or 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.

4.5 Interaction with other medicines and other forms of interaction

No drug interaction studies have been performed with Azarga.

Brinzolamide

Azarga 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.

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 used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (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

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 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. However, if Azarga is administered until delivery, the neonate should be carefully monitored during the first days of life.

Refer to section 5.3 for pre-clinical reproductive studies on brinzolamide and timolol.

Breast-feeding

It is not known whether brinzolamide is excreted in 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 ¹⁴C-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.

Fertility

There are no human data on the effects of Azarga on male or female fertility.

Refer to section 5.3 for pre-clinical studies on brinzolamide and timolol in fertility.

4.7 Effects on ability to drive and use machines

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 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 ($\geq 0.1\%$ to $< 1\%$): insomnia.

Nervous system disorders

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

Uncommon ($\geq 0.1\%$ 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 ($\geq 0.1\%$ to $< 1\%$): decreased blood pressure.

Respiratory, thoracic and mediastinal disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough.

Skin and subcutaneous tissue disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): hair disorder, lichen planus.

Post Marketing Experience

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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.

Blood and lymphatic system disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): white blood cell count decreased.

Psychiatric disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): insomnia.

Nervous system disorders

Common ($\geq 1\%$ to $< 10\%$): dysgeusia.

Eye disorders

Common ($\geq 1\%$ to $< 10\%$): punctate keratitis, blurred vision, eye pain, eye irritation.

Uncommon ($\geq 0.1\%$ 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 ($\geq 0.01\%$ to $< 0.1\%$): eyelid margin crusting.

Cardiac disorders

Common ($\geq 1\%$ to $< 10\%$): heart rate decreased.

Vascular disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): blood pressure decreased.

Respiratory, thoracic and mediastinal disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): cough.

Rare ($\geq 0.01\%$ to $< 0.1\%$): oropharyngeal pain, rhinorrhoea.

Renal and urinary disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): blood urine present.

General disorders and administration site conditions

Uncommon ($\geq 0.1\%$ to $< 1\%$): malaise.

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

Frequencies cannot be estimated from the available data.

Immune system disorders

Anaphylactic shock, hypersensitivity.

Cardiac disorders:

Palpitations.

Ear and labyrinth disorders

Tinnitus.

Psychiatric disorders

Hallucination, depression.

Nervous system disorders

Dizziness, headache, paraesthesia.

Eye disorders

Eye allergy, eyelid oedema, visual impairment, conjunctivitis.

Vascular disorders

Blood pressure increased.

Respiratory, thoracic and mediastinal disorders

Asthma, dyspnoea, epistaxis.

Gastrointestinal disorders

Abdominal pain upper, abdominal discomfort, diarrhoea, dry mouth, nausea.

Skin and subcutaneous tissue disorders

Alopecia, erythema, rash, pruritis.

Musculoskeletal and connective tissue disorders

Myalgia.

General disorders and administration site conditions

Chest pain, fatigue.

Investigations

Blood pressure increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensory organ; ophthalmologicals; antiglaucoma preparations and miotics; parasympathomimetics; ATC code: S01EC51.

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.

Pharmacodynamic effects

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 efficacy and safety

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 1 below.

Table 1: Mean IOP (mm/Hg)

Visit	Mean IOP (mmHg)							
	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 ± 3.29 μM , 18.1 ± 2.68 μM and 18.4 ± 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 $\text{AUC}_{0-12\text{h}}$ of timolol were 27% and 28% lower (C_{max} : 0.824 ± 0.453 ng/mL; $\text{AUC}_{0-12\text{h}}$: 4.71 ± 4.29 ng

h/mL), respectively in comparison to the administration of timolol 5 mg/mL (C_{max} : 1.13 ± 0.494 ng/mL; AUC_{0-12h} : 6.58 ± 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 ± 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.

Biotransformation

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.

Elimination

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

Carcinogenicity

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

Brinzolamide

A 2-year bioassay, in which 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 pheochromocytomas 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.

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).

Effects on 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.

Reproductive studies

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 fetal 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 fetuses 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. Embryofetal development studies with timolol maleate in mice and rabbits showed no evidence of embryofetal toxicity at oral doses up to 50 mg/kg/day. At higher doses, increases in resorptions and fetal variations (14 ribs and hypoplastic sternbrae) 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 sternbrae 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 fetuses 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 fetus/newborn child but bradycardia and arrhythmia have been reported in one case in the fetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride (0.1 mg in 1 mL) as a preservative

Mannitol

Carbomer 974P

Tyloxapol

Disodium edetate

Sodium chloride

Hydrochloric acid and/or sodium hydroxide (to adjust pH to approximately 7.2)

Purified water.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

24 months. Contents should be discarded four weeks after opening.

6.4 Special precautions for storage

Store Azarga Eye Drops below 25°C. Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

8 mL round opaque white low density polyethylene Drop-Tainer[®] bottle with polypropylene cap. The bottle contains 5 mL of suspension.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335

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9. DATE OF FIRST APPROVAL

21 January 2010.

10. DATE OF REVISION OF THE TEXT

29 July 2020

Summary Table of Changes

Section changed	Summary of new information
4.8	Addition of 'hallucination'
8	Sponsor address update

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