

1. NAME OF THE MEDICINAL PRODUCT

AZARGA® 10 mg/ml + 5 mg/ml eye drops,

suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 10 mg brinzolamide and 5 mg timolol (as timolol maleate).

Preservative: 1 ml of suspension contains 0.1 mg benzalkonium chloride.

For the full list of excipients: see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.

White to off-white uniform suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. (see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly

The dose is one drop of AZARGA® eye drops in the conjunctival sac of the affected eye(s) twice daily.

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

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

Use in paediatric patients

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

Use in geriatric patients

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

Use in patients with hepatic or renal impairment

No studies have been conducted with AZARGA eye drops or with timolol 5 mg/ml eye drops 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 eye drops 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 eye drops is therefore contraindicated in patients with severe renal impairment (see section 4.3).

Method of administration

For ocular use.

Instruct patients to shake the bottle well before use.

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.

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

To prevent contamination of the dropper tip and suspension, 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 the cap is removed, if the tamper evident snap collar is loose, remove it before using this product.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other beta-blockers.
- Hypersensitivity to sulphonamides (see section 4.4).
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure or cardiogenic shock.
- Severe allergic rhinitis.
- Severe renal impairment (see section 4.2).
- Hyperchloraemic acidosis (see section 4.2).

4.4 Special warnings and precautions for use

General

- Like other topically applied ophthalmic agents, brinzolamide and timolol are absorbed systemically. Due to the beta-blocker component, timolol, the same types of cardiovascular and pulmonary adverse reactions seen with systemic beta-blockers may occur. Due to the sulphonamide component, brinzolamide, the same types of undesirable effects that are attributable to sulphonamides may occur with topical administration.
- Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving AZARGA eye drops as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this product.
- 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.
- The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and oedema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Cardiac disorders

- 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 disorders

- Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of some ophthalmic beta-blockers.

Hypoglycaemia/diabetes

- Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

- Beta-blockers may also mask the signs of hyperthyroidism.

Muscle weakness

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

Other beta-blockers

- The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocker. The response of these patients should be closely observed. The use of two local beta-blockers or two local carbonic anhydrase inhibitors is not recommended (see section 4.5).

Mental alertness

- Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination. AZARGA eye drops is absorbed systemically and therefore this may occur with topical administration.

Anaphylactic reactions

- While taking beta-blockers, 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, acetazolamide) 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

- There is limited experience with AZARGA eye drops in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be utilised in treating these patients and close monitoring of the intraocular pressure is recommended.

- AZARGA eye drops has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.
- 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). Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended. 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.
- Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZARGA eye drops contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

Contact lenses

- AZARGA eye drops contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to the application of AZARGA eye drops and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

- No specific drug interaction studies have been performed with AZARGA eye drops.
- AZARGA eye drops 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 eye drops.
- 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. However, accumulation of brinzolamide is unlikely as renal elimination is the major route. 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 an ophthalmic beta-blocker is administered concomitantly with oral calcium channel blockers, beta-blockers, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine.
- 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 eye drops containing brinzolamide. The concomitant administration of AZARGA eye drops and oral carbonic anhydrase inhibitors has not been studied and is not recommended.
- The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when AZARGA eye drops is given to patients already receiving a systemic beta-blocker. The response of these patients should be closely observed. The use of two local beta-blockers or two local carbonic anhydrase inhibitors is not recommended.
- The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.
- Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.
- Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies have not been performed to evaluate the effect of topical ocular administration of AZARGA eye drops on human pregnancy. Brinzolamide administered orally showed no fetal malformations in rats or rabbits, but showed a decrease in fetal body weight and an increase in developmental variations in rats.

There are no adequate data regarding the use of ophthalmic brinzolamide and timolol in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. Epidemiological studies have not revealed malformative effects, but show a risk for intrauterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery.

AZARGA eye drops should not be used during pregnancy unless clearly necessary. However, if AZARGA eye drops is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

It is not known whether ophthalmic brinzolamide is excreted in human breast milk. Studies in animals have shown that following oral administration brinzolamide is excreted in breast milk.

Beta-blockers are excreted in breast milk having the potential to cause serious undesirable effects in the breastfeeding infant.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from AZARGA eye drops therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of AZARGA eye drops on human fertility.

Non-clinical data do not show any effects of either brinzolamide or timolol on male or female fertility.

No effects on male or female fertility are anticipated from the use of AZARGA eye drops.

4.7 Effects on ability to drive and use machines

AZARGA eye drops has minor influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. 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 (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

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 $< 1/1,000$), or very rare ($< 1/10,000$) or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness. The adverse reactions were obtained during clinical trials and postmarketing surveillance.

System Organ Classification	Adverse reactions MedDRA Preferred Term (v18.0)
Blood and lymphatic systems disorders	<i>Uncommon</i> : white blood cell count decreased
Psychiatric disorders	<i>Uncommon</i> : insomnia
Nervous system disorders	<i>Common</i> : dysgeusia
Eye disorders	<i>Common</i> : punctate keratitis vision blurred, eye pain, eye irritation <i>Uncommon</i> : keratitis, vital dye staining cornea present, dry eye, eye pruritus, foreign body sensation in eyes, eye discharge, ocular hyperaemia, blepharitis, allergic conjunctivitis, corneal disorder, conjunctival hyperaemia, asthenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis, <i>Rare</i> : corneal erosion, anterior chamber flare, photophobia, lacrimation increased, scleral hyperaemia, erythema of eyelid, eyelid margin crusting
Cardiac disorders	<i>Common</i> : heart rate decreased
Vascular disorders	<i>Uncommon</i> : blood pressure decreased
Respiratory, thoracic and mediastinal disorders	<i>Uncommon</i> : chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough <i>Rare</i> : oropharyngeal pain
Skin and subcutaneous tissue disorders	<i>Uncommon</i> : hair disorder, lichen planus
Renal and urinary disorders	<i>Uncommon</i> : blood urine present
General disorders and administration site conditions	<i>Uncommon</i> : malaise

Description of selected adverse reactions

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic adverse reaction associated with the use of AZARGA* eye drops during clinical trials. It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is attributable to brinzolamide. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

AZARGA eye drops contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same

type of adverse reactions attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

AZARGA* eye drops contains brinzolamide and timolol (as timolol maleate). Additional adverse reactions associated with the use of the individual components that may potentially occur with AZARGA eye drops include those detailed below. Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. The incidence of systemic adverse drug reactions after topical ophthalmic administration is lower than of systemic administration.

	Brinzolamide 10 mg/ml	Timolol 5 mg/ml
System Organ Classification	Adverse reactions	
Infections and infestations	nasopharyngitis, pharyngitis, sinusitis, rhinitis	
Blood and lymphatic system disorders	decreased red blood cell count, increased blood chloride	
Immune system disorders		systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders		hypoglycaemia
Psychiatric disorders	apathy, depression, depressed mood, decreased libido, nightmare, nervousness	nightmares, memory loss
Nervous system disorders	somnolence, motor dysfunction, amnesia, memory impairment, paraesthesia, tremor, hypoaesthesia, ageusia	cerebral ischaemia, cerebrovascular accident, syncope, increases in the signs and symptoms of myasthenia gravis, paresthesia, headache, dizziness
Eye disorders	keratitis, keratopathy, increased optic nerve cup/disc ratio, corneal epithelium defect, corneal epithelium disorder, increased intraocular pressure, eye deposit, corneal staining, corneal oedema, conjunctivitis, meibomianitis, diplopia, glare, photophobia, photopsia, reduced visual acuity, pterygium, ocular discomfort, keratoconjunctivitis sicca, hypoaesthesia of the eye, scleral pigmentation, subconjunctival cyst, increased lacrimation, visual disturbance, eye swelling, eye allergy, madarosis, eyelid disorder, eyelid oedema	signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), keratitis, choroidal detachment following filtration surgery, decreased corneal sensitivity, ptosis, diplopia
Ear and labyrinth disorders	tinnitus, vertigo	
Cardiac disorders	cardio-respiratory distress, angina pectoris, bradycardia,	bradycardia, chest pain, palpitations, oedema,

	irregular heart rate, arrhythmia, palpitations, tachycardia, increased heart rate	arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure
Vascular disorders	hypertension	hypotension, Raynaud's phenomenon, cold hands and feet
Respiratory, thoracic and mediastinal disorders	dyspnoea, asthma, bronchial hyperactivity, epistaxis, throat irritation, nasal congestion, upper respiratory tract congestion, postnasal drip, sneezing, nasal dryness	bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea
Gastrointestinal disorders	dry mouth, oesophagitis, vomiting, dyspepsia, abdominal pain, abdominal discomfort, stomach discomfort, frequent bowel movements, gastrointestinal disorder, oral hypoesthesia, oral paraesthesia, flatulence	nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting
Hepato-biliary disorders	abnormal liver function test	
Skin and subcutaneous tissue disorders	urticaria, maculo-papular rash, generalised pruritus, alopecia, skin tightness, dermatitis, erythema	alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders	back pain, muscle spasms, myalgia, arthralgia, pain in extremity	myalgia
Renal and urinary disorders	renal pain, pollakiuria	
Reproductive system and breast disorders	erectile dysfunction	sexual dysfunction, decreased libidoe
General disorders and administration site conditions	pain, asthenia, chest discomfort, fatigue, feeling abnormal, feeling jittery, irritability, chest pain, peripheral oedema, malaise, medication residue	asthenia/fatigue
Injury, poisoning and procedural complications	foreign body in eye	

Paediatric population

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

TABULATED LIST OF ADVERSE REACTIONS – POST-MARKETING SURVEILLANCE

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	Adverse reactions MedDRA Preferred Term (v18.0)
Immune system disorders	Anaphylactic shock ,hypersensitivity
Cardiac disorder Palpitations	Palpitations
Ear and labyrinth disorders	Tinnitus

Psychiatric disorders	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 discomfort, diarrhoea, dry mouth, nausea
Skin and subcutaneous tissue disorders	Alopecia, erythema, rash, pruritus
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Chest pain, fatigue

4.9 Overdose

An ocular overdose of AZARGA eye drops may be flushed from the eye(s) with lukewarm water.

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.

Treatment of an accidental ingestion should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics; ATC code: S01ED51

Mechanism of action

AZARGA eye drops 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. The combined effect of these two active substances results in additional IOP reduction compared to either compound alone.

Brinzolamide is a potent inhibitor of human carbonic anhydrase II (CA-II), the predominant iso-enzyme 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-blocker 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.

Pharmacodynamic effects

The active components of AZARGA®, 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® produces greater mean IOP

reductions than those produced by either AZOPT® (brinzolamide 1% ophthalmic suspension), or Timolol Maleate Ophthalmic Solution, 0.5% used alone.

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 eye drops dosed twice daily was 7 to 9 mmHg. The non-inferiority of AZARGA eye drops as compared to dorzolamide 20 mg/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

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 eye drops dosed twice daily was 7 to 9 mmHg, and was up to 3 mmHg greater than that of brinzolamide 10 mg/ml dosed twice daily and up to 2 mmHg greater than that of timolol 5 mg/ml 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.

In three controlled clinical trials, the ocular discomfort upon instillation of AZARGA eye drops was significantly lower than that of dorzolamide 20 mg/ml + timolol 5 mg/ml.

Pediatric Population:

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy (See Section 4.2).

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 eye drops administration. Following twice daily dosing of AZARGA eye drops in both eyes for 13 weeks, red blood cell (RBC) concentrations of brinzolamide averaged $18.8 \pm 3.29 \mu\text{M}$, $18.1 \pm 2.68 \mu\text{M}$ and $18.4 \pm 3.01 \mu\text{M}$ at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained (RBC saturation of CA-II at approximately $20 \mu\text{M}$).

At steady state, following administration of AZARGA eye drops, the mean plasma C_{max} and $\text{AUC}_{0-12\text{h}}$ of timolol were 27% and 28% lower (C_{max} : $0.824 \pm 0.453 \text{ ng/ml}$; $\text{AUC}_{0-12\text{h}}$: $4.71 \pm 2.49 \text{ ng}\cdot\text{h/ml}$), respectively, in comparison to the administration of timolol 5 mg/ml (C_{max} : $1.13 \pm 0.494 \text{ ng/ml}$; $\text{AUC}_{0-12\text{h}}$: $6.58 \pm 3.18 \text{ ng}\cdot\text{h/ml}$). The lower systemic exposure to timolol following AZARGA eye drops administration is not clinically relevant. Following administration of AZARGA eye drops, 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 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.

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

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 thiazolidine 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/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 eye drops.

Special populations and conditions

Paediatrics: AZARGA eye drops has not been evaluated in the paediatric population.

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

Gender: Following topical ocular administration of AZARGA eye drops, 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 eye drops.

Hepatic insufficiency: AZARGA eye drops has not been studied in patients with hepatic disease.

Renal insufficiency: AZARGA eye drops has not been studied in patients with renal impairment.

5.3 Preclinical safety data

Brinzolamide

Non-clinical data reveal no special hazard for humans with brinzolamide based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Developmental toxicity studies in rabbits with oral doses of brinzolamide of up to 6 mg/kg/day (214 times the recommended daily clinical dose of 28 µg/kg/day) revealed no effect on foetal development despite significant maternal toxicity. Similar studies in rats resulted in slightly reduced ossification of skull and sternebrae of foetuses of dams receiving brinzolamide at doses of 18 mg/kg/day (642 times the recommended daily clinical dose), but not 6 mg/kg/day. These findings occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. Dose-related decreases in foetal weights were observed in pups of dams receiving brinzolamide orally ranging from a slight decrease (about 5-6%) at 2 mg/kg/day to nearly 14% at 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

Timolol

Non-clinical data reveal no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (at 50 mg/kg/day or 3500 times the daily clinical dose of 14

µg/kg/day) and increased foetal resorptions in rabbits (at 90 mg/kg/day or 6400 times the daily clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, mannitol (E421), carbomer 974P, tyloxapol, disodium edetate, sodium chloride, hydrochloric acid and/or sodium hydroxide (for pH adjustment), purified water.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C.

Discard 4 weeks after first opening.

Do not use this medicine after the expiry date which is stated on the packaging.

Keep out of the reach and sight of children.

6.4 Nature and contents of container

Bottles with a dispensing plug and screw cap (DROPTAINER dispensing bottle) filled with 2.5 ml or 5 ml AZARGA eye drops.

Not all presentations may be registered/marketed.

6.5 Special precautions for disposal

No special requirements.

6.6 Manufacturer

See folding box

(Information issued: April 2016.SINv2)

Novartis Pharma AG, Basel, Switzerland