

AZARGA - Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

AZARGA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

One ml of suspension contains 0.10 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic suspension (eye drops)

White to off-white uniform suspension, pH 7.2 (approximately).

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 in the conjunctival sac of the affected eye(s) twice daily.

When using nasolacrimal occlusion or closing the eyelids, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity (see section 4.4).

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 medicinal product with AZARGA-, the other medicinal product should be discontinued and AZARGA should be started the following day.

Special populations

Paediatric population

The safety and efficacy of AZARGA in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Hepatic and renal impairment

No studies have been conducted with AZARGA 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 has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min) or in patients with hyperchloraemic acidosis (see section 4.3). Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA is therefore contraindicated in patients with severe renal impairment (see section 4.3).

AZARGA should be used with caution in patients with severe hepatic impairment (see section 4.4).

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use. After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and the 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.

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

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 not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.
- Severe allergic rhinitis.
- Hyperchloraemic acidosis (see section 4.2).
- Severe renal impairment.

4.4 Special warnings and precautions for use

Systemic effects

- Brinzolamide and timolol are absorbed systemically. Due to the beta-adrenergic blocking component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.
- Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving AZARGA as it is absorbed systemically.

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.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.

Muscle weakness

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

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. AZARGA should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

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.

Acid/base disturbances

AZARGA contains brinzolamide, a sulphonamide. The same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. This medicinal product should be used 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 the use of this medicinal product.

Mental alertness

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination. AZARGA 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.

Concomitant therapy

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

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 (see section 4.5).

Ocular effects

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

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

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

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. This may lead to a corneal decompensation and oedema and wearing contact lenses might increase the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

AZARGA may be used while wearing contact lenses with careful monitoring (see below under 'Benzalkonium chloride').

Benzalkonium chloride

AZARGA contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should 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.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Hepatic impairment

AZARGA should be used with caution in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with AZARGA.

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 receiving 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, 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 solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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 (see section 4.4).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. Caution is recommended in the concomitant use of this medicinal product with clonidine.

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. Caution is recommended.

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

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, see section 5.3. AZARGA should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine 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. If AZARGA 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, see section 5.3.

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

However, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AZARGA 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 on human fertility.

Non clinical data do not show any effects of either brinzolamide or timolol on male or female fertility, following oral dosing. No effects on male or female fertility are anticipated from the use of AZARGA.

4.7 Effects on ability to drive and use machines

AZARGA 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 machines.

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 clinical trials, the most common adverse reactions were blurred vision, eye irritation and eye pain, occurring in approximately 2% to 7% of patients.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies and post-marketing surveillance with AZARGA and the individual components brinzolamide and timolol. They 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 $< 1/1000$), very rare ($< 1/10,000$), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v. 18.0)
Infections and infestations	<u>Not known:</u> nasopharyngitis ³ , pharyngitis ³ , sinusitis ³ , rhinitis ³
Blood and lymphatic system disorders	<u>Uncommon:</u> white blood cell count decreased ¹ <i>Not known:</i> decreased red blood cell count ³ , increased blood chloride ³
Immune system disorders	<u>Not known:</u> anaphylaxis ² , anaphylactic shock ¹ , systemic allergic reactions including angioedema, ² localised and generalised rash ² , hypersensitivity ¹ , urticaria ² , pruritus ²
Metabolism and nutrition disorders	<u>Not known:</u> hypoglycaemia ²
Psychiatric disorders	<u>Rare:</u> insomnia ¹ <u>Not known:</u> hallucinations ² , depression ¹ , memory loss ² , apathy ³ , depressed mood ³ , decreased libido ³ , nightmare ^{2,3} , nervousness ³
Nervous system disorders	<u>Common:</u> dysgeusia ¹ <u>Not known:</u> cerebral ischaemia ² , cerebrovascular accident ² , syncope ² , increases in the signs and symptoms of myasthenia gravis ² , somnolence ³ , motor

	dysfunction ³ , amnesia ³ , memory impairment ³ , paraesthesia ^{2,3} , tremor ³ , hypoaesthesia ³ , ageusia ³ , dizziness ¹ , headache ¹
Eye disorders	<p><u>Common:</u> punctate keratitis¹, blurred vision¹, eye pain¹, eye irritation¹</p> <p><u>Uncommon:</u> keratitis^{1,2,3}, dry eye¹, vital dye staining cornea present¹, eye discharge¹, eye pruritus¹, foreign body sensation in eyes¹, ocular hyperaemia¹, conjunctival hyperaemia¹</p> <p><u>Rare:</u> corneal erosion¹, anterior chamber flare¹, photophobia¹, lacrimation increased¹, scleral hyperaemia¹, erythema of eyelid¹, eyelid margin crusting¹.</p> <p><u>Not known:</u> increased optic nerve cup/disc ratio³, choroidal detachment following filtration surgery² (see section 4.4 Special warnings and precautions for use), keratopathy³, corneal epithelium defect³, corneal epithelium disorder³, increased intraocular pressure³, eye deposit³, corneal staining³, corneal oedema³, decreased corneal sensitivity², conjunctivitis³, meibomianitis³, diplopia^{2,3}, glare³, photopsia³, reduced visual acuity³, visual impairment¹, pterygium³, ocular discomfort³, keratoconjunctivitis sicca³, hypoaesthesia of the eye³, scleral pigmentation³, subconjunctival cyst³, visual disturbance³, eye swelling³, eye allergy³, madarosis³, eyelid disorder³, eyelid oedema¹, ptosis².</p>
Ear and labyrinth disorders	<u>Not known:</u> vertigo ³ , tinnitus ³
Cardiac disorders	<p><u>Common:</u> heart rate decreased¹</p> <p><u>Not known:</u> cardiac arrest², cardiac failure², congestive heart failure², atrioventricular block², cardio-respiratory distress³, angina pectoris³, bradycardia^{2,3}, irregular heart rate³, arrhythmia^{2,3}, palpitations^{2,3}, tachycardia³, increased heart rate³, chest pain², oedema²</p>
Vascular disorders	<p><u>Uncommon:</u> decreased blood pressure¹</p> <p><u>Not known:</u> hypotension², hypertension³, blood pressure increased¹, Raynaud's phenomenon², cold hands and feet²</p>
Respiratory, thoracic and mediastinal disorders	<p><u>Uncommon:</u> cough¹</p> <p><u>Rare:</u> oropharyngeal pain¹, rhinorrhoea¹</p> <p><u>Not known:</u> bronchospasm² (predominantly in patients with pre-existing bronchospastic disease), dyspnoea¹, asthma³, epistaxis¹, bronchial hyperactivity³, throat irritation³, nasal congestion³,</p>

	upper respiratory tract congestion ³ , postnasal drip ³ , sneezing ³ , nasal dryness ³
Gastrointestinal disorders	<u>Not known</u> : vomiting ^{2,3} , abdominal pain upper ¹ , abdominal pain ² , diarrhoea ¹ , dry mouth ¹ , nausea ¹ , oesophagitis ³ , dyspepsia ^{2,3} , abdominal discomfort ³ , stomach discomfort ³ , frequent bowel movements ³ , gastrointestinal disorder ³ , oral hypoesthesia ³ , oral paraesthesia ³ , flatulence ³
Hepatobiliary disorders	<u>Not known</u> : abnormal liver function test ³
Skin and subcutaneous tissue disorders	<u>Not known</u> : urticaria ³ , maculo-papular rash ³ , generalised pruritus ³ , skin tightness ³ , dermatitis ³ , alopecia ¹ , psoriasiform rash or exacerbation of psoriasis ² , rash ¹ , erythema ¹
Musculoskeletal and connective tissue disorders	<u>Not known</u> : myalgia ¹ , muscle spasms ³ , arthralgia ³ , back pain ³ , pain in extremity ³
Renal and urinary disorders	<u>Uncommon</u> : blood urine present ¹ <u>Not known</u> : renal pain ³ , pollakiuria ³
Reproductive system and breast disorders	<u>Not known</u> : erectile dysfunction ³ , sexual dysfunction ² , decreased libido ²
General disorders and administration site conditions	<u>Uncommon</u> : malaise ^{1,3} <u>Not known</u> : chest pain ¹ , pain ³ , fatigue ¹ , asthenia ^{2,3} , chest discomfort ³ , feeling jittery ³ , irritability ³ , peripheral oedema ³ , medication residue ³
Investigations	<u>Uncommon</u> : blood potassium increase ¹ , blood lactate dehydrogenase increased ¹

¹ adverse reactions observed for AZARGA

² additional adverse reactions observed with timolol monotherapy

³ additional adverse reactions observed with brinzolamide monotherapy

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 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 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.

Timolol is absorbed into the systemic circulation. This may cause similar adverse reactions as seen with systemic beta-blocking medicinal products. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. Additional adverse reactions associated with the use of the individual components that may potentially occur with AZARGA are included in the table above. The incidence of systemic adverse reactions after

topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

4.9 Overdose

In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

If overdose with AZARGA eye drops occurs, treatment should be symptomatic and supportive. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antiglaucoma preparation and miotics
ATC code: S01ED51.

Mechanism of action

AZARGA contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated IOP primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. The combined effect of these two 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 adrenergic-blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Pharmacodynamic effects

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 dosed twice daily was 7 to 9 mmHg. 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 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 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[®], was significantly lower than that of 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, 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

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} : $0.824 \pm 0.453 \text{ ng/ml}$; $\text{AUC}_{0-12\text{h}}$: $4.71 \pm 4.29 \text{ ng}\cdot\text{h/ml}$), 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[®] 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 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[®]. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of AZARGA[®].

Biotransformation

The metabolic pathways for the metabolism of brinzolamide involve N-dealkylation, O-dealkylation 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 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.

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

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 sternbrae 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 3,500 times the daily clinical dose of 14 µg/kg/day) and increased foetal resorptions in rabbits (at 90 mg/kg/day or 6,400 times the daily clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Carbomer 974P,
Sodium chloride
Tyloxapol,
Benzalkonium chloride,
Disodium edetate,
Sodium hydroxide and/or Hydrochloric acid (for pH adjustment),
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

5 ml white and opaque low density polyethylene bottles with a dispensing plug and polypropylene screw cap containing 5 ml suspension.

Carton containing 1 bottle.

6.6 Special precautions for disposal

No special requirements.

7 Registration Number

145-12-32030

8 Registration holder AND Importer

Novartis Israel Ltd., P.O.B 7126, Tel Aviv

Revised on September 2020