NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

AZARGA® (10 mg/mL brinzolamide + 5 mg/mL timolol) 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.

If more than 1 topical ophthalmic medicinal product is used, the medicines must be administered at least 5 minutes apart.

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.

Patients should be instructed to shake the bottle well before use.

Nasolacrimal occlusion and closing the eyelids for 2 minutes after instillation is recommended. This may result in a decrease in systemic side effects and an increase in local activity.

Patients must be instructed to remove soft contact lenses prior to application of AZARGA® and to wait 15 minutes after instillation of the dose before reinsertion.

To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

After the cap is removed, if the tamper evident snap collar is loose, this should be removed before using the 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. Systemic absorption can be minimised by nasolacrimal occlusion (see section 4.2).
- 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 reported with sulphonamide derivates. including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving AZARGA eye drops as it is absorbed systemically. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs of serious reactions or hypersensitivity occur, use of this product should be discontinued immediately.
- Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. AZARGA® should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

- 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 edema. 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 IOP 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 (epinephrine) 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 (epinephrine). 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

- Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Patients should avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to the application of AZARGA® eye drops and to 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, it is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates) 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.
- Beta-blockers can decrease the response to adrenaline (epinephrine) used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy of anaphylaxis (see section 4.4).
- 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.There are no adequate data and well-controlled studies 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 hypoglycemia) have been observed in the neonate when systemic beta-blockers have been administered to the mother until delivery.

In reproductive toxicity studies, brinzolamide administered orally to rats during organogenesis induced fetal toxicity at 91 times the maximum recommended ophthalmic human dose (MROHD) based on body surface area (BSA). In rabbits, no fetal toxicity was observed following oral administration during organogenesis at 61 times the MROHD based on BSA. Reproduction studies in mice, rats and rabbits with orally administered timolol during organogenesis showed no malformations up to 254 times the MROHD based on BSA (see Animal data).

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

Animal data

No developmental and reproductive toxicity studies were performed with Azarga® (brinzolamide and timolol in combination).

Brinzolamide

Embryofetal development studies were conducted in pregnant rats administered 0, 2, 6 or 18 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 17 to target the period of organogenesis. Decreased maternal weight gain was observed at 6 and 18 mg/kg/day. Decreased fetal body weight and reduced skeletal ossification were observed at 18 mg/kg/day (91 times the MROHD based on BSA). The No-Observed effect level (NOEL) was 2 mg/kg/day (10 times the MROHD based on BSA).

Embryofetal development studies were conducted in pregnant rabbits administered 0, 1, 3, or 6 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Maternal weight loss during pregnancy was observed at 3 mg/kg/day (30 times the MROHD based on BSA) and above. At 6 mg/kg/day, mortality, emaciation, lack of feces and abortions were noted in does. The NOEL for maternal toxicity was 1 mg/kg/day (10 times the MROHD based on

BSA). No treatment-related fetal effects were observed up to the maximum tested dose of 6 mg/kg/day (61 times the MROHD based on BSA).

In a rat peri-/postnatal study, brinzolamide was orally administered at doses of 1, 5 and 15 mg/kg/day from gestation day 16 through lactation day 20. Decreases in food consumption and mean body weight gain was seen in parental dams during gestation and lactation at 15 mg/kg/day. Decreased pup body weight was observed at 15 mg/kg/day (76 times the MROHD based on BSA). The NOEL for maternal and developmental toxicity was 5 mg/kg/day (25 times the MROHD based on BSA).

Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and the levels of radioactivity in fetal tissues were 3- to 10-fold less than those measured in the dams.

Timolol

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (≥254 times the MROHD based on BSA) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, no adverse effects were noted on postnatal development of offspring. Doses of 1000 mg/kg/day (5085 times the MROHD based on BSA) were maternally toxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 mg/kg/day (2034 times the MROHD based on BSA), without apparent maternal toxicity.

Breast-feeding

There are no adequate data regarding the use of Azarga in breast-feeding women.

There are no data regarding the effects of brinzolamide and timolol on the breastfed infant, or milk production.

It is not known whether brinzolamide is transferred into human milk following topical ocular administration. Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

Timolol is transferred into human breast milk following ocular topical administration. Oral beta blockers have the potential to cause serious adverse reactions in the breastfed infant. However, in the case of ocular administration at therapeutic doses, the amounts of timolol present in breast milk are not likely to produce clinical symptoms of beta-blockade in the infant.
The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Azarga and any potential adverse effects on the breast-fed child from Azarga.
A decision must be made whether to discontinue breastfeeding 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® eye drops on human fertility. In a rat fertility study no adverse effects of brinzolamide on the fertility or reproductive capacity of males or females were observed at doses up to 18 mg/kg/day (91 times the MROHD based on BSA). Fertility studies with timolol in rats showed no effects at oral doses up to 150 mg/kg/day (1525 times the MROHD based on BSA).
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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 post-marketing surveillance.

System Organ Classification	Adverse reactions
Blood and lymphatic systems disorders	*Uncommon*: white blood cell count decreased
Psychiatric disorders	*Uncommon:* insomnia
Nervous system disorders	*Common:* dysgeusia
Eye disorders	*Common:* punctate keratitis vision blurred, eye pain, eye irritation
	Uncommon: keratitis, ocular hyperaemia, conjunctival hyperaemia, vital dye staining cornea present, dry eye, eye pruritus, foreign body sensation in eyes, eye discharge allergic conjunctivitis, corneal disorder, conjunctival hyperaemia, asthenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis,
	Rare: corneal erosion, anterior chamber flare, scleral hyperaemia, erythema of eyelid, lacrimation increased, eyelid margin crusting, photophobia
Cardiac disorders	*Common:* heart rate decreased
Vascular disorders	*Uncommon:* blood pressure decreased
Respiratory, thoracic and mediastinal disorders	*Uncommon:* chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough
	Rare: oropharyngeal pain
Skin and subcutaneous tissue disorders	*Uncommon:* hair disorder, lichen planus
Renal and urinary disorders	*Uncommon:* blood urine present
General disorders and administration site conditions	*Uncommon:* 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 hypoaesthesia, 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**
Immune system disorders	Anaphylactic shock ,hypersensitivity
Cardiac disorder Palpitations	Palpitations
Ear and labyrinth disorders	Tinnitus
Psychiatric disorders	Hallucination, depression
Nervous system disorders	Dizziness, paraesthesia, headache
Eye disorders	Visual impairment, eyelid edema, conjunctivitis,
Vascular disorders	Blood pressure increased
Respiratory, thoracic and mediastinal	asthma, dyspnoea, epistaxis
Gastrointestinal disorders	Diarrhoea, dry mouth, abdominal discomfort,
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), erythema, pruritus, alopecia, rash
Musculoskeletal and connective tissue	Myalgia
General disorders and administration	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.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics; ATC code:

S01ED51 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. 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 IOP 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 8 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 8 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 of AZARGA®, 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 ± 3.29 µM, 18.1 ± 2.68 µM and 18.4 ± 3.01 µM at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained (RBC saturation of CA-II at approximately 20 µM).

At steady state, following administration of AZARGA® eye drops, the mean plasma C_{max} and AUC_{0-12h} of timolol were 27% and 28% lower (C_{max}: 0.824 ± 0.453 ng/ml; AUC_{0-12h}: 4.71 ± 2.49 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® 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.

In humans, timolol is metabolized by cleavage of the morpholine ring to form two primary metabolites. There is an acetyl ethanol secondary amine derivative, which undergoes subsequent loss of the acetyl side chain to form an ethanolic primary amine analog. Hydroxylation of the terminal methyl group on the t-butyl moiety to form an alcohol is a minor metabolic pathway in humans. Timolol is primarily metabolized in the liver by the CYP2D6 isozyme. No timolol metabolism occurs within the eye.

Excretion/Elimination
Brinzolamide is eliminated primarily by renal excretion (approximately 60%). About 20% of the dose has been accounted for in urine as metabolites. 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 impairment.
Renal insufficiency: AZARGA® eye drops has not been studied in patients with renal impairment.

5.3 Preclinical safety data

Non-clinical data for brinzolamide and timolol reveal no special hazard for humans with brinzolamide based on conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential and topical ocular irritation studies. For information on reproductive and developmental toxicity, see section 4.6 Fertility, pregnancy and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, mannitol (E421), carbomer 974P, sodium chloride, tyloxapol, disodium edetate, 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, 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

Novartis Pharma AG, Basel, Switzerland

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