NOVARTIS

Regulatory Affairs

AZARGA®

(brinzolamide / timolol)

10 mg/mL brinzolamide / 5 mg/mL timolol

Eye drops, Suspension

Summary of Product Characteristics (SmPC)

Azarga®

Antiglaucoma preparation and miotics.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Eye drops, suspension.

Active substances

One mL of the eye drop suspension contains 10 mg of brinzolamide, and 6.8 mg timolol maleate corresponding to 5 mg of timolol.

Excipients

Excipient with known effect: 1 mL of the eye drop suspension contains 0.1 mg of benzalkonium chloride.

Other excipients: mannitol, carbomer 974P, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water

Pharmaceutical formulations may vary between countries.

INDICATIONS

Azarga® ophthalmic suspension is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction and when combination therapy is appropriate.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Adults

The dose is 1 drop of Azarga 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 medicinal product with Azarga, the other medicinal product should be discontinued and Azarga should be started the following day.

Special populations

Renal or hepatic impairment

No studies have been conducted with Azarga in patients with hepatic or renal impairment.

Pediatric patients (below 18 years)

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

Geriatric patients (65 years of age or above)

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

Method of administration

- For ocular use.
- Patients should be instructed to shake the bottle well before use.
- 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.
- Nasolacrimal occlusion and closing the eyelid 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.
- After cap is removed, if tamper evident snap collar is loose, this should be removed before using the product.

CONTRAINDICATIONS

- Hypersensitivity to the active substances, to any of the excipients or to sulphonamides.
- 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 renal impairment.
- Hyperchloraemic acidosis.

WARNINGS AND PRECAUTIONS

General

Like other topically applied ophthalmic agents, brinzolamide and timolol are absorbed systemically. Systemic absorption can be minimized by nasolacrimal occlusion (see section DOSAGE REGIMEN AND ADMINISTRATION).

Due to beta-adrenergic blocking component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur.

Hypersensitivity reactions reported with sulphonamide derivates, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving Azarga as it is absorbed systemically. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs of serious reactions or hypersensitivity occur, 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.

Hypoglycemia/diabetes

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

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Muscle weakness

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

Other beta-blocking agents

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-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section INTERACTIONS).

Anaphylactic reactions

While taking beta-blockers, patients with 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 dose 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 anesthesia

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

Contact lenses

Benzalkonium chloride may cause eye irritation and is known to discolor soft contact lenses. Patients should avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Azarga and to wait at least 15 minutes before reinsertion.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Blood and lymphatic system disorders	White blood cell count decreased	Uncommon
Psychiatric disorders	Insomnia	Rare
Nervous system disorders	Dysgeusia	Common
Eye disorders	Punctate keratitis, vision blurred, eye pain, eye irritation	Common
	Keratitis, ocular hyperaemia, conjunctival hyperaemia, vital dye staining cornea present, dry eye, eye pruritus, foreign body sensation in eyes, eye discharge	Uncommon
	Corneal erosion, anterior chamber flare, scleral hyperaemia, erythema of eyelid, lacrimation increased, eyelid margin crusting, photophobia.	Rare
Cardiac disorders	Heart rate decreased	Common
Vascular disorder	Blood pressure decreased	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
	Oropharyngeal pain, rhinorrhoea	Rare
Renal and urinary disorder	Blood urine present	Uncommon
General disorders and administration site conditions	Malaise	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Azarga via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Immune system disorders	Anaphylactic shock, hypersensitivity
Psychiatric disorders	Hallucination, depression
Nervous system disorders	Dizziness, paraesthesia, headache
Eye disorders	Visual impairment, eyelid oedema, conjunctivitis, eye allergy
Ear and labyrinth disorders	Tinnitus
Cardiac disorder	Palpitations

System organ classification	Adverse drug reaction
Vascular disorders	Blood pressure increased
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, epistaxis
Gastrointestinal disorders	Diarrhoea, dry mouth, abdominal discomfort, nausea
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), erythema, pruritus, alopecia, rash
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Chest pain, fatigue

INTERACTIONS

The following interactions are expected with Azarga due to potential drug interactions with the mono-components:

- Azarga contains brinzolamide, a carbonic anhydrase inhibitor and, although administered topically, it's absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates) must be considered in patients receiving Azarga.

- There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients 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.

- 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.

- 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), or digitalis glycosides, or parasympathomimetics.

- Beta-blockers can decrease the response to adrenaline (epinephrine) used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section WARNINGS AND PRECAUTIONS).

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies in pregnant women regarding the ocular use of Azarga or the individual components.

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 should not be used during pregnancy unless clearly necessary. However, if Azarga is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Data

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.

Lactation

Risk summary

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 breast-fed 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.

Females and males of reproductive potential

Infertility

Studies have not been performed to evaluate the effect of topical ocular administration of Azarga 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.

OVERDOSAGE

- 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 possible nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

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

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

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 humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Timolol is a non-selective beta-adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilizing 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.

Pharmacodynamics (PD)

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.

Pharmacokinetics (PK)

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 the start of administeringAzarga. Following twice daily dosing of Azarga 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). The mean steady-state timolol plasma C_{max} was 0.824 ng/mL and T_{max} was 0.79 hours after dosing withAzarga.

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.

Timolol can be measured in human aqueous humour after administration of timolol ophthalmic solution and in plasma for up to 12 hours after administration of Azarga.

Biotransformation/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.

Elimination

^{14}C Brinzolamide is eliminated primarily in urine and feces in comparable amounts, 32% and 29%, respectively. About 20% of the dose has been accounted for in urine as metabolites. Brinzolamide and N-desethyl-brinzolamide are the predominant components 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 is excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4.8 hours after administration of Azarga.

Special populations

Pediatric patients (below 18 years)

Azarga has not been evaluated in the pediatric population.

Geriatric patients (65 years of age or above)

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

Gender

Following topical ocular administration of Azarga, there were no clinically relevant differences in systemic exposure to brinzolamide, N-desethyl brinzolamide or timolol, when analyzed by gender.

Race/Ethnicity

No efficacy and safety differences due to ethnicity are expected with Azarga.

Renal impairment

Azarga has not been studied in patients with renal impairment.

Hepatic impairment

Azarga has not been studied in patients with hepatic impairment.

CLINICAL STUDIES

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 8 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 mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of Azarga 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 was significantly lower than that of dorzolamide 20 mg/mL + timolol 5 mg/mL.

NON-CLINICAL SAFETY DATA

Non-clinical data for brinzolamide and timolol reveal no special hazard for humans 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 PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Azarga must be kept out of the sight and reach of children.

Azarga should not be used after the date marked “EXP” on the pack.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

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