SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brinzolamide/Timolol AZAD 10 mg/ml + 5 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of suspension contains 10 mg brinzolamide and timolol maleate corresponding to 5 mg timolol.

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

Eye drops, 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 /.../ 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 /.../, the other medicinal product should be discontinued and /.../ should be started the following day.

Special populations

Paediatric population
The safety and efficacy of /.../ 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 /.../ 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.

/.../ 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, /.../ is therefore contraindicated in patients with severe renal impairment (see section 4.3).

/.../ 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 derivates can occur in patients receiving /.../ as it is absorbed systemically.
- Brinzolamide is a sulphonamide inhibitor of carbonic anhydrase and although administered topically, is absorbed systemically. The same types of adverse drug reactions that are attributable to sulphonamides may occur with topical administration, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). 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, brinzolamide should be withdrawn immediately.

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. /.../ 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
/.../ 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. /.../ 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.

<u>Concomitant therapy</u>
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 /.../. The concomitant administration of /.../ and oral carbonic anhydrase inhibitors has not been studied and is not recommended (see section 4.5).

Ocular effects
There is limited experience with /.../ 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.

/.../ 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.

/.../ may be used while wearing contact lenses with careful monitoring (see below under ‘Benzalkonium chloride’).

Benzalkonium chloride
/.../ contains benzalkonium chloride. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use. It 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 /.../ 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
/.../ 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 /.../.

/.../ 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 /.../.

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. /.../ 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 /.../ 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 /.../ 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 /.../ 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 /.../.

4.7 Effects on ability to drive and use machines

/.../ 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 /.../ and the individual components brinzolamide and timolol. They 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 <1/1000), 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	Not known: nasopharyngitis[3], pharyngitis[3], sinusitis[3], rhinitis[3]
Blood and lymphatic system disorders	Uncommon: white blood cell count decreased[1] Not known: decreased red blood cell count[3], increased blood chloride[3]
Immune system disorders	Not known: 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	Not known: hypoglycaemia[2]
Psychiatric disorders	Rare: insomnia[1] Not known: depression[1], memory loss[2], apathy[3], depressed mood[3], decreased libido[3], nightmare[2,3], nervousness[3], Hallucination[2]
Nervous system disorders	Common: dysgeusia[1] Not known: 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	Common: punctate keratitis[1], blurred vision[1], eye pain[1], eye irritation[1] Uncommon: keratitis[1,2,3], dry eye[1], vital dye staining cornea present[1], eye discharge[1], eye pruritus[1], foreign body sensation in eyes[1], ocular hyperaemia[1], conjunctival hyperaemia[1] Rare: corneal erosion[1], anterior chamber flare[1], photophobia[1], lacrimation increased[1], scleral hyperaemia[1], erythema of eyelid[1], eyelid margin crusting[1]

	Not known: increased optic nerve cup/disc ratio[3], choroidal detachment following filtration surgery[2] (see section 4), keratopathy[3], corneal epithelium defect[3], corneal epithelium disorder[3], increased intraocular pressure[3], eye deposit[3], corneal staining[3], corneal oedema[3], decreased corneal sensitivity[2], conjunctivitis[3], meibomianitis[3], diplopia[2, 3], glare[3], photopsia[3], reduced visual acuity[3], visual impairment[1], pterygium[3], ocular discomfort[3], keratoconjunctivitis sicca[3], hypoaesthesia of the eye[3], scleral pigmentation[3], subconjunctival cyst[3], visual disturbance[3], eye swelling[3], eye allergy[3], madarosis[3], eyelid disorder[3], eyelid oedema[1], ptosis[2]
Ear and labyrinth disorders	Not known: vertigo[3], tinnitus[3]
Cardiac disorders	Common: heart rate decreased[1] Not known: cardiac arrest[2], cardiac failure[2], congestive heart failure[2], atrioventricular block[2], cardio-respiratory distress[3], angina pectoris[3], bradycardia[2,3], irregular heart rate[3], arrhythmia[2,3], palpitations[2,3], tachycardia[3], increased heart rate[3], chest pain[2], oedema[2]
Vascular disorders	Uncommon: decreased blood pressure[1] Not known: hypotension[2], hypertension[3], blood pressure increased[1], Raynaud's phenomenon[2], cold hands and feet[2]
Respiratory, thoracic and mediastinal disorders	Uncommon: cough[1] Rare: oropharyngeal pain[1], rhinorrhoea[1] Not known: bronchospasm[2] (predominantly in patients with pre-existing bronchospastic disease), dyspnoea[1], asthma[3], epistaxis[1], bronchial hyperactivity[3], throat irritation[3], nasal congestion[3], upper respiratory tract congestion[3], postnasal drip[3], sneezing[3], nasal dryness[3]
Gastrointestinal disorders	Not known: 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 hypoaesthesia[3], oral paraesthesia[3], flatulence[3]
Hepatobiliary disorders	Not known: abnormal liver function test[3]
Skin and subcutaneous tissue disorders	Not known: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). (see section 4.4), 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	Not known: myalgia[1], muscle spasms[3], arthralgia[3], back pain[3], pain in extremity[3]
Renal and urinary disorders	Uncommon: blood urine present[1] Not known: renal pain[3], pollakiuria[3]
Reproductive system and breast disorders	Not known: erectile dysfunction[3], sexual dysfunction[2], decreased libido[2]

General disorders and administration site conditions	Uncommon: malaise[1,3] Not known: 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	Uncommon: blood potassium increase[1], blood lactate dehydrogenase increased[1]

1 adverse reactions observed for /.../
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 /.../ 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).

/.../ 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 /.../ 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
/.../ 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 /.../ 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
/.../ 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 /.../ dosed twice daily was 7 to 9 mmHg. The non-inferiority of /.../ 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 /.../ 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 /.../ 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 /.../ administration. Following twice daily dosing of /.../ 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

At steady state, following administration of /.../, the mean plasma Cmax and AUC0-12h of timolol were 27% and 28% lower (Cmax: 0.824 ± 0.453 ng/ml; AUC0-12h: 4.71 ± 4.29 ng·h/ml), respectively, in comparison to the administration of timolol 5 mg/ml (Cmax: 1.13 ± 0.494 ng/ml; AUC0-12h: 6.58 ± 3.18 ng·h/ml). The lower systemic exposure to timolol following /.../ administration is not clinically relevant. Following administration of /.../, mean Cmax 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 /.../. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of /.../.

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 t1/2 of timolol is 4.8 hours after administration of /.../.

5.3 Preclinical safety data

Brinzolamide
Non-clinical data reveal no special hazard for humans with brinzolamide based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

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

Timolol
Non-clinical data reveal no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (at 50 mg/kg/day or 3500 times the daily clinical dose of 14 µg/kg/day) and increased foetal resorptions in rabbits (at 90 mg/kg/day or 6400 times the daily clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Mannitol (E421)
Carbomer
Disodium edetate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

4 weeks after first opening

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 ml low density polyethylene (LDPE) bottle, with a LDPE insert dropper and a high density polyethylene (HDPE) cap containing 5 ml suspension.

Cartons contain 1, 3 or 6 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AZAD Pharma GmbH,
Fritz-Reichle-Ring 6 A,
78315 Radolfzell am Bodensee,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2024-12-04