SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ZOMRANIP-T 1% + 0.5% Eye Drops, Suspension
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml suspension contains:
Active substance(s):
Brinzolamide 10mg/ml
Timolol 5 mg/ml (equivalent to 6.8 mg timolol maleate)
Excipient(s) with known effect:
Benzalkonium chloride 0.1 mg/ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye drops, suspension.
White to white-off ophthalmic suspension.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It 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.

4.2 Posology and method of administration
Posology/frequency and duration of administration
The dose is 1 drop of ZOMRANIP-T in the conjunctival sac of the affected eye(s) twice daily.

After instillation, gently closing the eyelids or nasolacrimal occlusion is recommended. This administration may reduce systemic absorption and thus the systemic adverse reactions of ocular medicinal products.

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.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed 1 drop in the affected eye (s) twice daily.

When substituting another ophthalmic antiglaucoma medicinal product with ZOMRANIP-T, the other medicinal product should be discontinued and ZOMRANIP-T should be started the following day.

Method of administration
For ocular use.

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

Additional information on special populations

Renal/Hepatic impairment

No studies have been conducted with brinzolamide/timolol 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.

Brinzolamide/timolol has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min) or in patients with hyperchloremic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, ZOMRANIP-T is therefore contraindicated in patients with severe renal impairment (see section 4.3).

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

Pediatric patients

The safety and efficacy of ZOMRANIP-T in children and adolescents aged 0 to 18 years have not yet been established. No data is available.

4.3 Contraindications

- Hypersensitivity to the active substances or to any excipients
- 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 pacemaker, overt cardiac failure, or cardiogenic shock.
- Severe allergic rhinitis
- Hypersensitivity to other beta-blockers
- Hyperchloremic acidosis (see section 4.2).
- Severe renal impairment
- Hypersensitivity to sulfonamides (see section 4.4).

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.

After instillation it is recommended to close the eyelids and apply gentle pressure on the nasolacrimal canaliculi. This may reduce the systemic absorption of ocular medicinal products, resulting in a decrease in systemic side effects and an increase in local activity.

Heart failure should be adequately controlled before starting timolol therapy. Patients with a history of severe heart disease should be monitored for signs of heart failure and have their pulse checked.

Hypersensitivity reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal

necrolysis (TEN) reported with sulphonamide derivates can occur in patients receiving brinzolamide/timolol 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, ZOMRANIP-T should be withdrawn immediately.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. If signs of serious reactions or hypersensitivity occur, discontinue the use of this medicinal product. ZOMRANIP-T should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

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

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide/timolol. The concomitant administration of brinzolamide/timolol and oral carbonic anhydrase inhibitors has not been studied and is not recommended (see section 4.5).

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. Beta-blockers may cause worsening of Prinzmetal's angina, severe peripheral and central circulatory disturbances, and hypotension. It should be used with caution in patients with first-degree heart block because it reduces conduction rate.
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.

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

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.

Acid/base disturbances

ZOMRANIP-T contains brinzolamide, a sulfonamide. 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. Brinzolamide/timolol is absorbed systemically and therefore this may occur with topical administration.

Hyperthyroidism
Beta-blockers may 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 generalized weakness).

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. The anesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy
Timolol may interact with other medicinal products (see section 4.5).
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when brinzolamide/timolol is given to the patients already receiving an oral beta-adrenergic blocker. The response of these patients should be closely observed. The concomitant use of two topical beta-adrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended (see section 4.5).

Anaphylactic reactions
While taking beta-adrenergic blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Ocular effects
There is limited experience with brinzolamide/timolol in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be exercised in treating these patients and close monitoring of intraocular pressure is recommended.

Brinzolamide/timolol 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 and wearing contact lenses might increase the risk for the cornea. Carbonic anhydrase inhibitors may affect corneal hydration and 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.

ZOMRANIP-T should be used with caution in patients with severe hepatic impairment.

Benzalkonium chloride
Benzalkonium chloride, widely used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since ZOMRANIP-T contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

ZOMRANIP-T contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lenses prior to the application of ZOMRANIP-T and wait 15 minutes after instillation of the dose before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been conducted with ZOMRANIP-T.

ZOMRANIP-T 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 ZOMRANIP-T.

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. 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 eye drops containing timolol are 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. 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.

Beta-adrenergic blocking agents may increase the hypoglycemic effect of antidiabetic agents. Beta-adrenergic blocking agents can mask the signs and symptoms of acute hypoglycemia (see section 4.4).

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

Additional information on special populations
Interaction studies have not been conducted.

Pediatric patients
Interaction studies have not been conducted.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category is “C”.

Women of child-bearing potential/Birth control (Contraception)
Women of childbearing potential are recommended to use effective contraception during treatment under medical supervision.

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). ZOMRANIP-T should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see Section 4.2.

Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide/timolol on human pregnancy. Oral administration of brinzolamide did not cause fetal malformations in rats or rabbits, but decreased fetal body weight and increased developmental variations were observed in rats.

Well-controlled epidemiologic studies of the systemic use of beta-adrenergic blocking agents have not shown malformational effects, but have shown a risk of intrauterine growth retardation with oral beta-blockers. Signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when beta-blockers have been administered until delivery. Data from a limited number of drug-exposed

pregnancies have not shown adverse effects of timolol eye drops on pregnancy or fetal/neonatal health; however, in one case, bradycardia and arrhythmias were reported in the fetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological information is available.

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

Data from animal studies are insufficient to draw conclusions regarding effects on pregnancy and/or embryonic/fetal development and/or postnatal development (see section 5.3). The potential risk for humans is unknown. ZOMRANIP-T should not be used during pregnancy unless necessary (except when deemed absolutely necessary by the physician).

Breastfeeding
It is unknown whether 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).

Timolol is excreted into 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 taking into account the benefit of breast-feeding for the child and the benefit of ZOMRANIP-T therapy for the mother.

Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide/timolol on human fertility. Non-clinical data do not show any effects of either brinzolamide or timolol on male or female fertility following oral dosing. Reproductive toxicity studies with brinzolamide or timolol do not indicate any particular hazard to humans.

4.7 Effects on ability to drive and use machines
As with all eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should be advised to wait until the vision clears before driving or using machines.

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination (see section 4.4). For this reason, patients should be advised not to drive until their vision is clear and they do not have these problems.

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

ZOMRANIP-T contains brinzolamide and timolol (equivalent to timolol maleate). The following adverse reactions have been reported during clinical studies and post-marketing surveillance with the individual active substances:

The frequency is described as follows: 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); not known (cannot be estimated from available data).

The adverse reactions observed when using a combination of two agents are listed in descending order of severity.

Infections and infestations
Not known: Nasopharyngitis, pharyngitis, sinusitis, rhinitis

Blood and lymphatic system disorders
Uncommon: White blood cell count decreased
Not known: Decreased red blood cell count, increased blood chloride

Immune system disorders
Not known: Anaphylactic shock, anaphylaxis, systemic allergic reactions (including angioedema), localized and generalized rash, hypersensitivity, urticaria, pruritus

Metabolism and nutrition disorders
Not known: Hypoglycemia

Psychiatric disorders
Rare: Insomnia
Not known: Hallucinations, depression, memory loss, apathy, depressed mood, decreased libido, nightmares, nervousness

Nervous system disorders
Common: Dysgeusia (disturbed taste)
Not known: Cerebral ischemia, cerebrovascular accident, syncope, increases in the signs and symptoms of myasthenia gravis, somnolence, motor dysfunction, memory loss, memory impairment, tremor, hypoesthesia, ageusia, dizziness, headache, paresthesia (numbness)

Eye disorders
Common: Blurred vision, eye pain, eye irritation, punctate keratitis
Uncommon: Dry eye, eye discharge, eye pruritus, ocular hyperemia, conjunctival hyperemia, foreign body sensation in eyes, keratitis
Rare: Corneal erosion, photophobia, scleral hyperemia, lacrimation increased, anterior chamber flare, erythema of eyelid
Not known: Increased optic nerve cup/disc ratio, choroidal detachment following filtration surgery (see section 4.4), keratitis, keratopathy, corneal epithelium defect, corneal epithelial disorder, increased intraocular pressure, eye deposit, corneal staining, corneal edema, decreased corneal sensitivity, conjunctivitis, meibomianitis, diplopia, glare, photopsia, reduced visual acuity, visual impairment, pterygium, ocular discomfort, keratoconjunctivitis sicca, hypoesthesia of the eye, scleral pigmentation, subconjunctival cyst, visual disturbance, eye swelling, eye allergy, madarosis, eyelid disorder, eyelid edema, ptosis

Ear and labyrinth disorders
Not known: Tinnitus, vertigo

Cardiac disorders
Common: Decreased heart rate
Not known: Cardiac arrest, cardiac failure, congestive heart failure, atrioventricular block, cardio-respiratory distress, angina pectoris, bradycardia, irregular heart rate, arrhythmia, palpitations, tachycardia, increased heart rate, chest pain, edema

Vascular disorders
Uncommon: Decreased blood pressure
Not known: Hypotension, hypertension, increased blood pressure, Raynaud's phenomenon, cold hands and feet

Respiratory, thoracic and mediastinal disorders
Uncommon: Cough
Rare: Oropharyngeal pain, rhinorrhea
Not known: Asthma, dyspnea, epistaxis, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), bronchial hyperactivity, throat irritation, nasal congestion, upper respiratory tract congestion, postnasal drip, sneezing, nasal dryness

Gastrointestinal disorders
Not known: Abdominal discomfort, stomach discomfort, oral hypoesthesia (decreased oral sensitivity), diarrhea, dry mouth, nausea, vomiting, upper abdominal pain, abdominal pain, esophagitis, dyspepsia, frequent bowel movements, gastrointestinal disorder, oral paresthesia, flatulence

Hepatobiliary disorders
Not known: Abnormal liver function tests

Skin and subcutaneous tissue disorders
Not known: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.4), alopecia, erythema, pruritus, rash, urticaria, maculo-papular rash, generalized pruritus, skin tightness, dermatitis, psoriasiform rash or exacerbation of psoriasis

Musculoskeletal, connective tissue, and bone disorders
Not known: Myalgia, muscle spasm, arthralgia, back pain, pain in extremity

Renal and urinary tract disorders
Uncommon: Blood urine present
Not known: Renal pain, pollakiuria

Reproductive system and breast disorders
Not known: Erectile dysfunction, decreased libido, sexual dysfunction

General disorders and administration site conditions
Uncommon: Malaise
Not known: Chest pain, fatigue, pain, asthenia, weakness, chest discomfort, feeling jittery, irritability, nervousness, peripheral edema, medication residue

Investigations
Uncommon: Blood potassium increased, blood lactate dehydrogenase increased

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

ZOMRANIP-T contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, hematological, 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 ZOMRANIP-T 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose and treatment
If overdose with ZOMRANIP-T eye drops occurs, treatment should be symptomatic and supportive. 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 dialyze readily.
In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiglaucoma preparations and miotics
ATC code: S01ED51

Mechanism of action
ZOMRANIP-T contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated intraocular pressure (IOP) primarily by reducing aqueous humor 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 humor 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 brinzolamide/timolol dosed twice daily was 7 to 9 mmHg. The non-inferiority of brinzolamide/timolol 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 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 brinzolamide/timolol 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 brinzolamide/timolol was significantly lower than that of dorzolamide 20 mg/ml + timolol 5 mg/ml.

5.2 Pharmacokinetic properties
General 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 brinzolamide/timolol administration. Following twice daily dosing of brinzolamide/timolol 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 (saturation of RBC CA-II, approximately 20 µM).

At steady state, following administration of brinzolamide/timolol, 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 ± 4.29 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 brinzolamide/timolol administration is not clinically relevant. Following administration of brinzolamide/timolol, 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 humor up to 48 hours after administration of brinzolamide/timolol. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of brinzolamide/timolol.

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 metabolized 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 rena excretion (approximately 60%). About 20% of the dose the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethyl-brinzolamide are the predominant components found in the urine along with trace levels (<1%) of the N-desmethoxypropyl and O-desmethyl metabolites.

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4.8 hours after administration of brinzolamide/timolol.
Linearity/non-linearity:
No linearity/non-linearity data is available.

5.3 Preclinical safety data
Brinzolamide
Non-clinical data reveal no special hazard for humans with brinzolamide based on single-dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, and topical ocular irritation studies.

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 fetal development despite significant maternal toxicity. Similar studies in rats resulted in slightly reduced ossification of skull and sternebrae of fetuses 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 fetal weights. Dose-related decreases in fetal 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 is 5 mg/kg/day.

Timolol
Non-clinical data reveal no special hazard for humans with timolol based on single-dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, and topical ocular

irritation studies.

Reproduction toxicity studies with timolol showed delayed fetal ossification in rats with no adverse effects on postnatal development (at 50 mg/kg/day or 3500 times the daily clinical dose of 14 □g/kg/day) and increased fetal 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
Carbomer 974 P
Tyloxapol
Disodium EDTA
Sodium chloride
Hydrochloric acid and sodium hydroxide (pH adjuster)
Water for injection

6.2 Incompatibilities

None

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep at room temperature below 25°C.
Once opened, the product should be used within 28 days if kept at room temperature below 25ºC.

6.5 Nature and contents of container

Primary packaging of the product: Opaque, white, low density polyethylene (LDPE) bottle containing 5 mL of eye drops, with LDPE dropper tip and white HDPE screw cap. Each cardboard box includes 1 bottle and a package leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2023/525

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization : 20.12.2023
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT

20.12.2023