

**Summary of Product Characteristics  
(Product Data Sheet)**

<b>Name of the Medical Product</b>	
<b>Product Name: BRINZOX T (Brinzolamide 1% w/v and Timolol 0.5% w/v Ophthalmic Suspension)</b>	
<b>Pharmaceutical Dosage Form : Ophthalmic Suspension</b>	
<b>Composition:</b>	
Brinzolamide USP	1.0% w/v
Timolol Maleate BP	
Equivalent to Timolol	0.5 % w/v
Benzalkonium Chloride USPNF (As Preservative)	0.01% w/v
Sterile Aqueous Vehicle	q.s.
<b>Pharmaceutical Form:</b>	
Ophthalmic Suspension White to off white coloured, aqueous suspension.	
<b>List of Excipients:</b>	
Benzalkonium Chloride USPNF, Tyloxapol USP, Carbomer Homopolymer USPNF, Mannitol BP Disodium Edetate BP, Sodium Chloride BP, Sodium Hydroxide BP, Water for Injection IP / BP / IH / USP	
<b>Clinical Particulars</b>	
<b>Therapeutic Indications:</b>	
Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.	
<b>Posology and Method of administration:</b>	
<b>Posology</b>	
<u>Use in adults, including the elderly:</u>	
The dose is one drop of Brinzolamide/Timolol 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.	
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 Brinzolamide/Timolol, the other medicinal product should be discontinued and Brinzolamide/Timolol should be started the following day.	

**Special populations****Paediatric population**

The safety and efficacy of Brinzolamide/Timolol in children and adolescents aged 0 to 18 years has not yet been established. No data is available.

**Hepatic and renal impairment**

No studies have been conducted with Brinzolamide/Timolol or with timolol 5mg/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.

Brinzolamide/Timolol 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, Brinzolamide/Timolol is therefore contraindicated in patients with severe renal impairment.

Brinzolamide/Timolol should be used with caution in patients with severe hepatic impairment.

**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.

**Contraindications:**

- Hypersensitivity to the active substances or to any of the excipients.
- Hypersensitivity to other beta-blockers.
- Hypersensitivity 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 not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.
- Severe allergic rhinitis
- Hyperchloraemic acidosis.
- Severe renal impairment.

**Special warning 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.

- Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving Brinzolamide/Timolol as it is absorbed systemically.

#### Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

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

#### Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

#### Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.

#### Muscle weakness

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

#### Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Brinzolamide/Timolol 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

Brinzolamide/Timolol 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. Brinzolamide/Timolol is absorbed systemically and therefore this may occur with topical administration.

#### Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic

reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

#### Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

#### Surgical anaesthesia

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

#### Concomitant therapy

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

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.

#### Ocular effects

There is limited experience with Brinzolamide/Timolol 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.

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. This may lead to a corneal decompensation and edema 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.

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

#### Benzalkonium chloride

Brinzolamide/Timolol 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 Brinzolamide/Timolol 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

Brinzolamide/Timolol should be used with caution in patients with severe hepatic impairment.

#### **Interactions with other medicinal products and other forms of Interactions :**

No specific drug interaction studies have been performed with Brinzolamide/Timolol.

Brinzolamide/Timolol 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 Brinzolamide/Timolol.

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.

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.

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

#### **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. Brinzolamide/Timolol should not be used during pregnancy unless clearly necessary.

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 Brinzolamide/Timolol 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.

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.

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 Brinzolamide/Timolol 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 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. No effects on male or female fertility are anticipated from the use of Brinzolamide/Timolol.

#### **Effects on ability to drive and use machine:**

Brinzolamide/Timolol 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.

#### **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 Brinzolamide/Timolol and the individual components brinzolamide and timolol. They are classified according to the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), 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
<i>Infections and infestations</i>	<u>Not known</u> : nasopharyngitis <sup>3</sup> , pharyngitis <sup>3</sup> , sinusitis <sup>3</sup> , rhinitis <sup>3</sup>
<i>Blood and lymphatic system disorders</i>	<u>Uncommon</u> : white blood cell count decreased <sup>1</sup> <u>Not known</u> : decreased red blood cell count <sup>3</sup> , increased blood chloride <sup>3</sup>
<i>Immune system disorders</i>	<u>Not known</u> : anaphylaxis <sup>2</sup> , anaphylactic shock <sup>1</sup> , systemic allergic reactions including angioedema <sup>2</sup> , localised and generalised rash <sup>2</sup> , hypersensitivity <sup>1</sup> , urticaria <sup>2</sup> , pruritus <sup>2</sup>
<i>Metabolism and nutrition disorders</i>	<u>Not known</u> : hypoglycaemia <sup>2</sup>
<i>Psychiatric disorders</i>	<u>Rare</u> : insomnia <sup>1</sup> <u>Not known</u> : depression <sup>1</sup> , memory loss <sup>2</sup> , apathy <sup>3</sup> , depressed mood <sup>3</sup> , decreased libido <sup>3</sup> , nightmare <sup>2,3</sup> , nervousness <sup>3</sup> , Hallucination*
<i>Nervous system disorders</i>	<u>Common</u> : dysgeusia <sup>1</sup> <u>Not known</u> : cerebral ischaemia <sup>2</sup> , cerebrovascular accident <sup>2</sup> , syncope <sup>2</sup> , increases in the signs and symptoms of myasthenia gravis <sup>2</sup> , somnolence <sup>3</sup> , motor dysfunction <sup>3</sup> , amnesia <sup>3</sup> , memory impairment <sup>3</sup> , paraesthesia <sup>2,3</sup> , tremor <sup>3</sup> , hypoaesthesia <sup>3</sup> , ageusia <sup>3</sup> , dizziness <sup>1</sup> , headache <sup>1</sup>
<i>Eye disorders</i>	<u>Common</u> : punctate keratitis <sup>1</sup> , blurred vision <sup>1</sup> , eye pain <sup>1</sup> , eye irritation <sup>1</sup> <u>Uncommon</u> : keratitis <sup>1,2,3</sup> , dry eye <sup>1</sup> , vital dye staining cornea present <sup>1</sup> , eye discharge <sup>1</sup> , eye pruritus <sup>1</sup> , foreign body sensation in eyes <sup>1</sup> , ocular hyperaemia <sup>1</sup> , conjunctival hyperaemia <sup>1</sup> <u>Rare</u> : corneal erosion <sup>1</sup> , anterior chamber flare <sup>1</sup> , photophobia <sup>1</sup> , lacrimation increased <sup>1</sup> , scleral hyperaemia <sup>1</sup> , erythema of eyelid <sup>1</sup> , eyelid margin crusting <sup>1</sup> <u>Not known</u> : increased optic nerve cup/disc ratio <sup>3</sup> , choroidal detachment following filtration surgery <sup>2</sup> , keratopathy <sup>3</sup> , corneal epithelium defect <sup>3</sup> , corneal epithelium disorder <sup>3</sup> , increased intraocular pressure <sup>3</sup> , eye deposit <sup>3</sup> , corneal staining <sup>3</sup> , corneal oedema <sup>3</sup> , decreased corneal sensitivity <sup>2</sup> , conjunctivitis <sup>3</sup> , meibomianitis <sup>3</sup> , diplopia <sup>2,3</sup> , glare <sup>3</sup> , photopsia <sup>3</sup> , reduced visual acuity <sup>3</sup> , visual impairment <sup>1</sup> , pterygium <sup>3</sup> , ocular discomfort <sup>3</sup> , keratoconjunctivitis sicca <sup>3</sup> , hypoaesthesia of the eye <sup>3</sup> , scleral pigmentation <sup>3</sup> , subconjunctival cyst <sup>3</sup> , visual disturbance <sup>3</sup> , eye swelling <sup>3</sup> , eye allergy <sup>3</sup> , madarosis <sup>3</sup> , eyelid disorder <sup>3</sup> , eyelid oedema <sup>1</sup> , ptosis <sup>2</sup>
<i>Ear and labyrinth disorders</i>	<u>Not known</u> : vertigo <sup>3</sup> , tinnitus <sup>3</sup>
<i>Cardiac disorders</i>	<u>Common</u> : heart rate decreased <sup>1</sup>

	<u>Not known</u> : cardiac arrest <sup>2</sup> , cardiac failure <sup>2</sup> , congestive heart failure <sup>2</sup> , atrioventricular block <sup>2</sup> , cardio-respiratory distress <sup>3</sup> , angina pectoris <sup>3</sup> , bradycardia <sup>2,3</sup> , irregular heart rate <sup>3</sup> , arrhythmia <sup>2,3</sup> , palpitations <sup>2,3</sup> , tachycardia <sup>3</sup> , increased heart rate <sup>3</sup> , chest pain <sup>2</sup> , oedema <sup>2</sup>
<i>Vascular disorders</i>	<u>Uncommon</u> : decreased blood pressure <sup>1</sup> <u>Not known</u> : hypotension <sup>2</sup> , hypertension <sup>3</sup> , blood pressure increased <sup>1</sup> , Raynaud's phenomenon <sup>2</sup> , cold hands and feet <sup>2</sup>
<i>Respiratory, thoracic and mediastinal disorders</i>	<u>Uncommon</u> : cough <sup>1</sup> <u>Rare</u> : oropharyngeal pain <sup>1</sup> , rhinorrhoea <sup>1</sup> <u>Not known</u> : bronchospasm <sup>2</sup> (predominantly in patients with pre-existing bronchospastic disease), dyspnoea <sup>1</sup> , asthma <sup>3</sup> , epistaxis <sup>1</sup> , bronchial hyperactivity <sup>3</sup> , throat irritation <sup>3</sup> , nasal congestion <sup>3</sup> , upper respiratory tract congestion <sup>3</sup> , postnasal drip <sup>3</sup> , sneezing <sup>3</sup> , nasal dryness <sup>3</sup>
<i>Gastrointestinal disorders</i>	<u>Not known</u> : vomiting <sup>2,3</sup> , abdominal pain upper <sup>1</sup> , abdominal pain <sup>2</sup> , diarrhoea <sup>1</sup> , dry mouth <sup>1</sup> , nausea <sup>1</sup> , oesophagitis <sup>3</sup> , dyspepsia <sup>2,3</sup> , abdominal discomfort <sup>3</sup> , stomach discomfort <sup>3</sup> , frequent bowel movements <sup>3</sup> , gastrointestinal disorder <sup>3</sup> , oral hypoesthesia <sup>3</sup> , oral paraesthesia <sup>3</sup> , flatulence <sup>3</sup>
<i>Hepatobiliary disorders</i>	<u>Not known</u> : abnormal liver function test <sup>3</sup>
<i>Skin and subcutaneous tissue disorders</i>	<u>Not known</u> : urticaria <sup>3</sup> , maculo-papular rash <sup>3</sup> , generalised pruritus <sup>3</sup> , skin tightness <sup>3</sup> , dermatitis <sup>3</sup> , alopecia <sup>1</sup> , psoriasiform rash or exacerbation of psoriasis <sup>2</sup> , rash <sup>1</sup> , erythema <sup>1</sup>
<i>Musculoskeletal and connective tissue disorders</i>	<u>Not known</u> : myalgia <sup>1</sup> , muscle spasms <sup>3</sup> , arthralgia <sup>3</sup> , back pain <sup>3</sup> , pain in extremity <sup>3</sup>
<i>Renal and urinary disorders</i>	<u>Uncommon</u> : blood urine present <sup>1</sup> <u>Not known</u> : renal pain <sup>3</sup> , pollakiuria <sup>3</sup>
<i>Reproductive system and breast disorders</i>	<u>Not known</u> : erectile dysfunction <sup>3</sup> , sexual dysfunction <sup>2</sup> , decreased libido <sup>2</sup>
<i>General disorders and administration site conditions</i>	<u>Uncommon</u> : malaise <sup>1,3</sup> <u>Not known</u> : chest pain <sup>1</sup> , pain <sup>3</sup> , fatigue <sup>1</sup> , asthenia <sup>2,3</sup> , chest discomfort <sup>3</sup> , feeling jittery <sup>3</sup> , irritability <sup>3</sup> , peripheral oedema <sup>3</sup> , medication residue <sup>3</sup>
<i>Investigations</i>	<u>Uncommon</u> : blood potassium increase <sup>1</sup> , blood lactate dehydrogenase increased <sup>1</sup>

<sup>1</sup> adverse reaction observed for Brinzolamide/Timolol

<sup>2</sup> additional adverse reactions observed with timolol monotherapy

<sup>3</sup> additional adverse reactions observed with brinzolamide monotherapy

**Overdosage:**

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

If overdose with Brinzolamide/Timolol 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.

**Pharmacological properties**
**Pharmacodynamic Properties:**
**Mechanism of Action**

Brinzolamide/Timolol 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 isoenzyme 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.

**Pharmacokinetics 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 (1mg) 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  $18.8 \pm 3.29\mu\text{M}$ ,  $18.1 \pm 2.68\mu\text{M}$  and  $18.4 \pm 3.01\mu\text{M}$  at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained

At steady state, following administration of Brinzolamide/Timolol, the mean plasma  $C_{\text{max}}$  and AUC 0-12h of timolol were 27% and 28% lower ( $C_{\text{max}}$ :  $0.824 \pm 0.453\text{ng/ml}$ ; AUC 0-12h:  $4.71 \pm 4.29\text{ng}\cdot\text{h/ml}$ ), respectively, in comparison to the administration of timolol 5mg/ml ( $C_{\text{max}}$ :  $1.13 \pm 0.494\text{ng/ml}$ ; AUC 0-12h:  $6.58 \pm 3.18\text{ng}\cdot\text{h/ml}$ ). The lower systemic exposure to timolol following Brinzolamide/Timolol administration is not clinically relevant. Following administration of Brinzolamide/Timolol, mean  $C_{\text{max}}$  of timolol was reached at  $0.79 \pm 0.45$  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 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 metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. Timolol metabolism is mediated primarily by CYP2D6.

#### Elimination

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

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma t<sub>1/2</sub> of timolol is 4.8 hours after administration of Brinzolamide/Timolol.

#### **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 6mg/kg/day (214 times the recommended daily clinical dose of 28µg/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 18mg/kg/day (642 times the recommended daily clinical dose), but not 6mg/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 2mg/kg/day to nearly 14% at 18mg/kg/day. During lactation, the no adverse effect level in the offspring was 5mg/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 50mg/kg/day or 3500 times the daily clinical dose of 14µg/kg/day) and increased foetal resorptions in rabbits (at 90mg/kg/day or 6400 times the daily clinical dose).

<b>Pharmaceutical particulars</b>
<b>Incompatibilities:</b> Not applicable
<b>Shelf life:</b> 3 Years
<b>Special Precautions for storage:</b> Use the suspension within four weeks after opening the vial.
<b>Storage Condition:</b> Do not store above 30°C.
<b>Nature and contents of container:</b> Opaque low-density polyethylene of 5 ml bottle with open translucent open nozzle, plastic closure and HDPE cap packed in carton along with pack insert.
<b>Marketing Authorization Holder:</b> Manufacturing Site : Ajanta Pharma Ltd. Mirza - Palashbhari Road, Village Kokhjar, Kamrup (R), Guwahati, Assam – 781128  Registered office: Ajanta House, Charkop, Kandivli (W), Mumbai 400 067 India.
<b>Marketing Authorization Numbers:</b> Not Applicable
<b>Date of first authorization/ renewal of the authorization:</b> Not Applicable
<b>Date of revision of text:</b> Nov 2021