1. NAME OF THE MEDICINAL PRODUCT

ZOPHER-PLUS EYE DROPS

(Brinzolamide and Timolol Ophthalmic Suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Declaration:

Brinzolamide and Timolol Ophthalmic Suspension

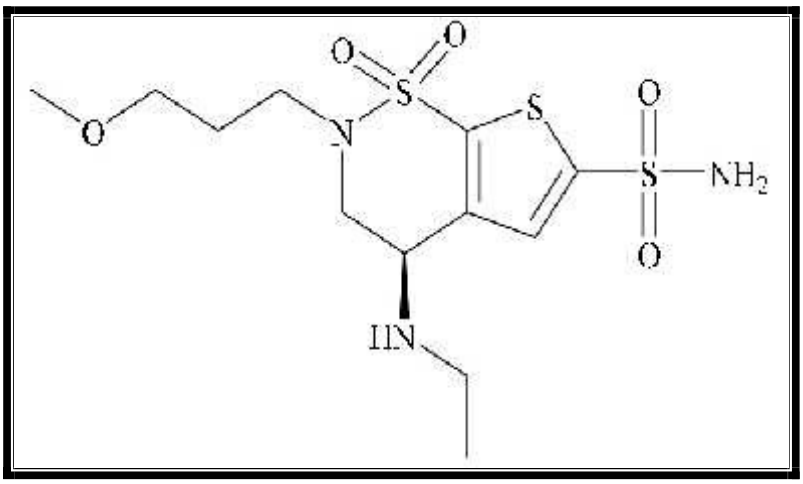
- **Brinzolamide:**

Chemical Name:
(4*R*)-4-(ethylamino)-2-(3-methoxypropyl)-1, 1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide

Molecular weight: 383.496 g/mol

Molecular formula: $C_{12}H_{21}N_3O_5S_3$

Structural Formula:-



- **Timolol Maleate:**

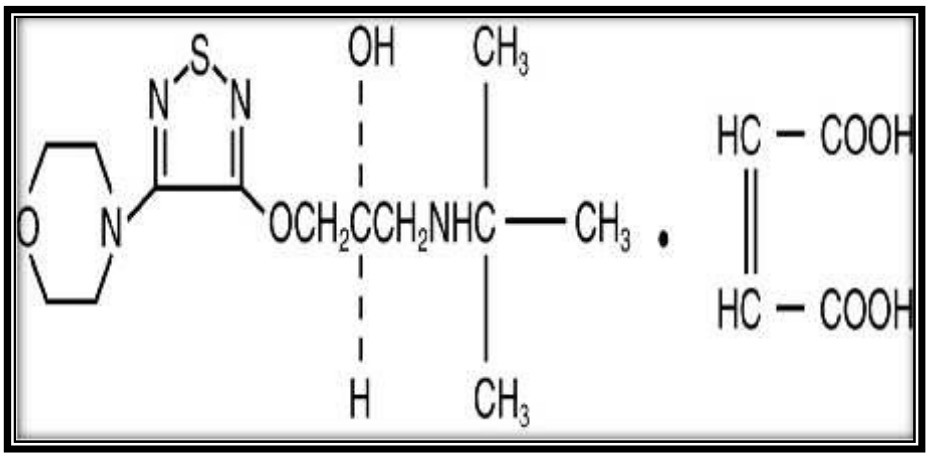
Chemical Name:

(2S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol

Molecular weight: 432.49 g/mol

Molecular formula: $C_{13}H_{28}N_4O_7S$

Structural Formula:-



Pharmaceutical Form Visual description of the appearance of product:
White to pale yellow coloured, homogeneous suspension.

Quantitative Declaration:

Composition:

Brinzolamide	USP	1.0% w/v
Timolol Maleate	USP	
Equivalent to Timolol		0.5% w/v
Benzalkonium Chloride	NF	0.01% w/v
(As Preservative)		
Sterile aqueous vehicle		Q.S

3. PHARMACEUTICAL FORM

Eye Drops

4. Clinical particulars

4.1 Therapeutic indications

INDICATIONS AND USAGE
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

DOSAGE AND ADMINISTRATION

Posology

Use in adults, including the elderly:

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 (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 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 (see section 4.3). Since brinzolamide and its main metabolite are excreted predominantly by the kidney, Brinzolamide/Timolol is therefore contraindicated in patients with severe renal impairment (see section 4.3).

Brinzolamide/Timolol 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 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 (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).

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 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 (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 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. Brinzolamide/Timolol 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 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, 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 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.

4.7 Effects on ability to drive and use machines

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 (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 Brinzolamide/Timolol 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 <1/1,000), 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 (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*
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: 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 reaction observed for Brinzolamide/Timolol

[2] additional adverse reactions observed with timolol monotherapy

[3] additional adverse reactions observed with brinzolamide monotherapy

* adverse reactions observed with timolol

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 Brinzolamide/Timolol 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).

Brinzolamide/Timolol 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 Brinzolamide/Timolol 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

Brinzolamide/Timolol 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacodynamic properties:
Pharmacotherapeutic group: Ophthalmologicals, Antiglaucoma preparation and miotics

ATC code: S01ED51

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 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 Brinzolamide/Timolol dosed twice daily was 7 to 9 mmHg. The non-inferiority of Brinzolamide/Timolol as compared to dorzolamide 20mg/ml + timolol 5mg/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 Brinzolamide/Timolol dosed twice daily was 7 to 9 mmHg, and was up to 3 mmHg greater than that of brinzolamide 10mg/ml dosed twice daily and up to 2 mmHg greater than that of timolol 5mg/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 20mg/ml + timolol 5mg/ml.

BRINZOLAMIDE:

Pharmacodynamic properties:

Used in the treatment of glaucoma, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Brinzolamide can decrease intraocular pressure by approximately 16-19% in patients with elevated intraocular

pressure.

Brinzolamide is a sulfonamide and carbonic anhydrase inhibitor with specific affinity for carbonic anhydrase II. Following topical ocular administration, Brinzolamide inhibits carbonic anhydrase II, an enzyme that is responsible for the movement of sodium and fluid transport in the eye. This inhibition leads to a decrease in aqueous humor secretion, probably by slowing the formation of bicarbonate ions, and results in a reduction in intraocular pressure. Brinzolamide is used to treat increased pressure in the eye caused by open-angle glaucoma.

Brinzolamide is a sulfonamide and a thienothiazine. It has a role as an antiglaucoma drug and an EC 4.2.1.1 (carbonic anhydrase) inhibitor.

Mechanism of action:

Brinzolamide is a highly specific inhibitor of CA-II, which is the main CA isoenzyme involved in the secretion of aqueous humor. Inhibition of CA in the ciliary process of the eye slows the formation of bicarbonate, and reduces sodium and fluid transport. This results in a reduction in the rate of aqueous humor secretion and the intraocular pressure. Brinzolamide is absorbed systemically following topical ocular administration. Since it has a high affinity for CA-II, brinzolamide binds extensively to red blood cells, where CA-II is primarily found. As sufficient CA-II activity remains, adverse effects resulting from the systemic inhibition of CA by brinzolamide are not observed. The metabolite N-desethyl brinzolamide is also formed. This metabolite binds to CA and accumulates in red blood cells as well. In the presence of brinzolamide, the metabolite binds mainly to carbonic anhydrase I (CA-I).

Application:

Brinzolamide is a highly specific, non-competitive, reversible carbonic anhydrase inhibitor. Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II). 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. The result is a reduction in intraocular pressure. Brinzolamide is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

TIMOLOL MALEATE EQ. TO TIMOLOL:

Pharmacodynamic properties:

Similar to propranolol and nadolol, timolol is a non-selective, beta-adrenergic receptor antagonist. Timolol does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity, but does possess a relatively high degree of lipid solubility. Timolol, when applied topically to the eye, has the action of reducing elevated, as well

as normal, intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage.

Mechanism of action:

Timolol maleate is a beta1 and beta2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function. Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Timolol Maleate Ophthalmic Solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of Timolol Maleate Ophthalmic Solution can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of Timolol Maleate Ophthalmic Solution is well maintained.

The precise mechanism of the ocular hypotensive action of Timolol Maleate Ophthalmic Solution is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Application:

This medication is used to treat high pressure inside the eye due to glaucoma (open angle-type) or other eye diseases (e.g., ocular hypertension). Lowering high pressure inside the eye helps to prevent blindness. This medication works by decreasing the amount of fluid within the eye. Timolol belongs to a class of drugs known as beta-blockers.

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 (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 ± 3.29µM, 18.1 ± 2.68µM and 18.4 ± 3.01µM 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 Cmax and AUC 0-12h of timolol were 27% and 28% lower (Cmax: 0.824 ± 0.453ng/ml; AUC 0-12h: 4.71 ± 4.29ng· h/ml), respectively, in comparison to the administration of timolol 5mg/ml (Cmax: 1.13 ± 0.494ng/ml; AUC 0-12h: 6.58 ± 3.18ng· h/ml). The lower systemic exposure to timolol following Brinzolamide/Timolol administration is not clinically relevant. Following administration of Brinzolamide/Timolol, 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 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 t1/2 of timolol is 4.8 hours after administration of Brinzolamide/Timolol.

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 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MATERIAL NAME	SPECS.
BENZALKONIUM CHLORIDE (95%)	NF
PROPYLENE GLYCOL	USP
CARBOMER (CARBOPOL 974P)	BP
BORIC ACID	NF
MANNITOL	USP
SODIUM CHLORIDE	BP/USP/ NF
TYLOXAPOL	USP/NF
SODIUM HYDROXIDE PELLETS	NF
PURIFIED WATER	BP/IH

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 degrees C.
Do not freeze.
Protect from light.
Keep out of the reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

The liquid is filled in a multi dose container, and contain Benzalkonium Chloride (95%), Propylene Glycol, Carbomer (Carbopol 974 P), Boric Acid, Mannitol, Sodium Chloride, Tyloxapol, and Sodium Hydroxide Pellets for pH Adjustment.
Solution is filled in 5 ml Opaque sterile plastic bottle (LDPE).

6.6 Special precautions for disposal <and other handling>

No special requirements

7. <APPLICANT/MANUFACTURER>

Applicant

KORLYNS PHARMACEUTICALS LTD.
No 31B, Adeyemi Adeoye Street,
Off Adeyemi Adeoye Road,
Opposite Health Centre, Wasimi,
Maryland, Lagos.
Telephone: 09064597759

Manufactured By:

Name and Address of Manufacturer:
INDIANA OPHTHALMICS
135, 136-137 Phase 2 GIDC,
Wadhwancity - 363035
Surendranagar
Gujarat – India
Tel: +91 2752 241554