Product Name: Zoladin Ophthalmic Suspension
(Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension, 1%/0.2%w/v)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

1.1 Product Name: Zoladin Ophthalmic Suspension

1.2 Strength: Provided in quality and quantitative composition

1.3 Pharmaceutical Dosage Form: Ophthalmic Suspension

2. Qualitative and Quantitative Composition:

2.1 Qualitative Declaration

2.2 Quantitative Declaration

Name of Ingredients	**Standard Reference**	**Quantity**			**Overage**	**Function**
Active Ingredients		**Per 100 ml**	**Per ml**	**In%**		
Brimonidine Tartrate	BP	0.200 g	0.002 g	0.2%	2.5%	Active Pharmaceutical Ingredient
Brinzolamide (Sterile & Micronized)	USP	1.000 g	0.010 g	1.0%	2.5%	Active Pharmaceutical Ingredient
Excipients						
Hydroxypropyl Methylcellulose (4000 cPs) (Methocel K4M CR Premium)	USP	0.500 g	0.005 g	0.50%	-	Suspending agent
Propylene Glycol	BP	1.000 g	0.010 g	1.00%	-	Water miscible co-solvent
Mannitol	BP	1.000 g	0.010 g	1.00%	-	Tonicity agent
Tyloxapol	USP	0.100 g	0.001 g	0.10%	-	Surfactant
Sodium Chloride	BP	0.200 g	0.002 g	0.20%	-	Tonicity agent
Boric Acid	BP	0.150 g	0.0015 g	0.15%	-	Buffering agent
Sodium Perborate	BP	0.10 g	0.0001 g	0.10%	-	Preservative
Sodium Hydroxide or Hydrochloric Acid	BP	q. s to adjust pH within 6.0 – 7.0	q. s to adjust pH within 6.0 – 7.0	q. s to adjust pH within 6.0 – 7.0	-	For pH adjustment
Water for Injections	BP	q. s. to 100.0 ml	q. s. to 1.0 ml	q. s. to 100.00%	-	Solvent

Note: 2.5% Overage for both Brimonidine Tartrate & Brinzolamide has been included in the product to compensate for expected and documented manufacturing losses.

3. Pharmaceutical Form :

Pharmaceutical form: An almost white to light yellow color suspension.

4. Clinical Particulars:

4.1 Therapeutic indications:

Zoladin Ophthalmic Suspension is indicated for decrease of elevated 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

Use in adults, including the elderly

The recommended dose is one drop of Zoladin in the affected eye(s) two times daily.

Hepatic and/or renal impairment

Zoladin has not been studied in patients with hepatic impairment and caution is therefore recommended in this population.

Zoladin has not been studied in patients with severe renal impairment (CrCl < 30mL/min) or in patients with hyperchloraemic acidosis.

Since the Brinzolamide component of Zoladin and its metabolite are excreted predominantly by the kidney, Zoladin is contraindicated in such patients.

Paediatric population

The safety and efficacy of Zoladin in children and adolescents aged 2 to 17 years has not been established.

Zoladin is not recommended in children or adolescents.

Zoladin must not be used in neonates and infants aged less than 2 years because of safety concerns

Method of administration

Ocular use.

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

When using nasolacrimal occlusion and closing the eyelids for 2 minutes, the systemic absorption is reduced.

This may result in a decrease in systemic side effects and an increase in local activity.

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Patients should be instructed to keep the bottle tightly closed when not in use.

Zoladin may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart.

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) 2 times daily.

4.3 Contraindications:

• Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1or to sulphonamides.

• Patients receiving monoamine oxidase (MAO) inhibitor therapy

• Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

• Patients with severe renal impairment

• Patients with hyperchloraemic acidosis

• Neonates and infants under the age of 2 years

4.4 Special warning and precautions for use:

The medicinal product should not be injected. Patients should be instructed not to swallow ZOLADIN.

Ocular effects ZOLADIN has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

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. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended. ZOLADIN may be used while wearing contact lenses with careful monitoring.

Brimonidine tartrate may cause ocular allergic reactions. If allergic reactions are observed, treatment should be discontinued. Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate, with some reported to be associated with an increase in IOP.

The potential effects following cessation of treatment with ZOLADIN have not been studied. While the duration of IOP-lowering effect for ZOLADIN has not been studied, the IOP-lowering effect of brinzolamide is expected to last for 5-7 days. The IOP-lowering effect of brimonidine may be longer.

Systemic effects

ZOLADIN contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. The same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. If signs of serious reactions or hypersensitivity occur, the use of this medicinal product should be discontinued.

Cardiac disorders

Following administration of ZOLADIN, small decreases in blood pressure were observed in some patients. Caution is advised when using medicinal products such as antihypertensives and/or cardiac glycosides concomitantly with ZOLADIN or in patients with severe or unstable and uncontrolled cardiovascular disease.

ZOLADIN should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Acid/base disturbances

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. ZOLADIN contains brinzolamide, aninhibitor of carbonic anhydrase, and although administered topically, is absorbed systemically. The sametypes of adverse reactions that are attributable to oral carbonic inhibitors (i.e., acid-base disturbances) may occur with topical administration.

Use with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. ZOLADIN is contraindicated in patients with severe renal impairment.

Hepatic impairment

ZOLADIN has not been studied in patients with hepatic impairment; caution should be used in treating such patients.

Mental alertness

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination in elderly patients. ZOLADIN is absorbed systemically and therefore this may occur with topical administration.

Paediatric population

The safety and efficacy of ZOLADIN in children and adolescents aged 2 to 17 years has not been established. Symptoms of brimonidine overdose (including loss of consciousness, hypotension, hypotonia, bradycardia, hypothermia, cyanosis and apnoea) have been reported in neonates and infants receiving brimonidine eye drops as part of medical treatment of

congenital glaucoma. ZOLADIN is therefore contraindicated in children below 2 years of age.

Treatment of children 2 years and above (especially in those in the 2-7 age range and/or weighing < 20 kg) is not recommended because of the potential for central nervous system-related side effects.

4.5 Undesirable effects:

Summary of the safety profile

In clinical trials involving ZOLADIN dosed twice-daily the most common adverse reactions were ocular hyperaemia and ocular allergic type reactions occurring in approximately 6-7% of patients, and dysgeusia (bitter or unusual taste in the mouth following instillation) occurring in approximately 3% of patients.

The safety profile of ZOLADIN was similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL).

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies with ZOLADIN twice-dailydosing and during clinical studies and post-marketing surveillance with the individual components brinzolamide and brimonidine.

They are classified according to the subsequent 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.

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System Organ Classification	**Adverse reactions**
Infections and infestations	Uncommon: nasopharyngitis2, pharyngitis2, sinusitus2 Not known: rhinitis2
Blood and lymphatic system disorders	Uncommon: red blood cell decreased2, blood chloride increased
Immune system disorders	Uncommon: hypersensitivity
Psychiatric disorders	Uncommon: apathy 2, depression2,3, depressed mood2, insomnia1, libido decreased2, nightmare2, nervousness2
Nervous system disorders	Common: somnolence, dizziness3, dysgeusia1 Uncommon: headache1, motor dysfunction2, amnesia2, memory impairment2, paraesthesia

	Very rare: syncope Not known: tremor2, hypoaesthesia2, ageusia2
Eye disorders	Common: eye allergy 1,keratitis1,eye pain1,ocular discomfort1, blurred vision1, abnormal vision3, ocular hyperaemia1, conjunctival blanching 3 Uncommon: corneal erosion1, corneal oedema 2, blepharitis 1,corneal deposits (keratic precipitates) 1, conjunctival disorder (papillae)1,photophobia1,photopsia\2, Eye swelling 2, eyelid oedema1, conjunctival oedema 1, dry eye,eye discharge, visual acuity reduced, lacrimation increased1, pterygium, erythema of eyelid, meibomianitis, diplopia, glare, hypoaesthesia eye, scleral pigmentation, subconjunctival cyst, abnormal sensation In eye asthenopia Very rare: uveitis, miosis Not known: visual disturbances, madarosis Ear and labyrinth Disorder: Uncommon: vertigo, tinitus

Description of selected adverse reactions Dysgeusia was the most common systemic adverse reaction associated with the use of ZOLADIN (3.4%). It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is mainly attributable to brinzolamide component of ZOLADIN. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect ZOLADIN

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.

Adverse reactions commonly associated with the brimonidine component of ZOLADINinclude the development of ocular allergic type reactions, fatigue and/or drowsiness, and dry mouth. The use of brimonidine has been associated with minimal decreases in blood pressure. Some patients who dosed with ZOLADIN experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

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.

4.6 Overdose and special antidotes:

System Organ Classification	**Adverse reactions**
Infections and infestations	Uncommon: nasopharyngitis2, pharyngitis2, sinusitus2 Not known: rhinitis2
Blood and lymphatic system disorders	Uncommon: red blood cell decreased2, blood chloride increased
Immune system disorders	Uncommon: hypersensitivity
Psychiatric disorders	Uncommon: apathy 2, depression2,3, depressed mood2, insomnia1, libido decreased2, nightmare2, nervousness2
Nervous system disorders	Common: somnolence, dizziness3, dysgeusia1 Uncommon: headache1, motor dysfunction2, amnesia2, memory impairment2, paraesthesia Very rare: syncope Not known: tremor2, hypoaesthesia2, ageusia2
Eye disorders	Common: eye allergy 1,keratitis1,eye pain1,ocular discomfort1, blurred vision1, abnormal vision3, ocular hyperaemia1, conjunctival blanching 3 Uncommon: corneal erosion1, corneal oedema 2, blepharitis 1,corneal deposits (keratic precipitates) 1, conjunctival disorder (papillae)1,photophobia1,photopsia\2, Eye swelling 2, eyelid oedema1, conjunctival oedema 1, dry eye,eye discharge, visual acuity reduced, lacrimation increased1, pterygium, erythema of eyelid, meibomianitis, diplopia, glare, hypoaesthesia eye, scleral pigmentation, subconjunctival cyst, abnormal sensation In eye asthenopia Very rare: uveitis, miosis Not known: visual disturbances, madarosis Ear and labyrinth Disorder: Uncommon: vertigo, tinitus

Description of selected adverse reactions Dysgeusia was the most common systemic adverse reaction associated with the use of ZOLADIN (3.4%). It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is mainly attributable to brinzolamide component of ZOLADIN. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect ZOLADIN 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.

Adverse reactions commonly associated with the brimonidine component of ZOLADIN include the development of ocular allergic type reactions, fatigue and/or drowsiness, and dry mouth. The use of brimonidine has been associated with minimal decreases in blood pressure. Some patients who dosed with ZOLADIN experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

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.

No case of overdose has been reported. Acute overdosage is unlikely to occur via the ophthalmic route.

4.7 Fertility, pregnancy and lactation

Fertility
Nonclinical data do not show any effects of brinzolamide or brimonidine on fertility.
There are no data on the effect of topical ocular administration of ZOLADIN on human fertility.

Pregnancy
There are no or limited amount of data from the use of ZOLADIN in pregnant women. Brinzolamide was teratogenic in rats, but not rabbits, following systemic administration. Animal studies with oral brimonidine do not indicate direct harmful effects with respect to reproductive toxicity. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ZOLADIN is not recommended during pregnancy and in women of child bearing potential not using contraception.

Lactation
It is unknown whether topical ZOLADIN is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown that following oral administration, minimal levels of brinzolamide are excreted in breast milk. Brimonidine administered orally is excreted in breast milk.
ZOLADIN should not be used by women nursing infants.

4.8 Effects on ability to drive and use machines

ZOLADIN has a moderate influence on the ability to drive and use machines.
ZOLADIN may cause dizziness, fatigue and/or drowsiness, which may impair the ability to drive or 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.
Oral carbonic anhydrase inhibitors may impair the ability of elderly patients to perform tasks requiring mental alertness and/or physical coordination.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

ZOLADIN contains two active substances: brinzolamide and brimonidine tartrate. These two components lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) by suppressing the formation of aqueous humour from the ciliary process in the eye. Although both brinzolamide and brimonidine lower IOP by suppressing aqueous humour formation, their mechanisms of action are different.
Brinzolamide acts by inhibiting the enzyme carbonic anhydrase (CA-II) in the ciliary epithelium that reduces the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport across the ciliary epithelium, resulting in decreased aqueous humour formation. Brimonidine, an alpha-2 adrenergic agonist, inhibits the enzyme adenylate cyclase and suppresses the cAMP-dependent formation of aqueous humour. Additionally, administration of brimonidine results in an increase in uveoscleral outflow.

5.2 Pharmacokinetic Properties:

Absorption
Brinzolamide is absorbed through the cornea following topical ocular administration. The Substance is also absorbed into the systemic circulation where it binds strongly to carbonic anhydrase in red blood cells (RBCs). Plasma concentrations are very low. Whole blood elimination half-life is prolonged (>100 days) in humans due to RBC carbonic anhydrase binding.

Brimonidine is rapidly absorbed into the eye following topical administration. In rabbits, maximum ocular concentrations were achieved in less than one hour in most cases. Maximum human plasma concentrations are < 1ng/mL and achieved within < 1 hour. Plasma levels decline with a half-life of approximately 2-3 hours. No accumulation occurs during chronic administration.
In a topical ocular clinical study comparing the systemic pharmacokinetics of ZOLADIN administered two or three times daily to brinzolamide and brimonidine administered individually using the same two posologies, the steady-state whole blood brinzolamide and N-desethylbrinzolamide pharmacokinetics were similar between the combination product and brinzolamide administered alone. Likewise, the steady-state plasma pharmacokinetics of brimonidine from the combination was similar to that observed for brimonidine administered alone with the exception of the twice daily ZOLADIN treatment group, for which the mean AUC0-12 hours was about 25% lower than that for brimonidine alone administered twice daily.

Distribution

Studies in rabbits showed that maximum brinzolamide ocular concentrations following topical administration are in the anterior tissues such as cornea, conjunctiva, aqueous humour and iris-ciliary body. Retention in ocular tissues is prolonged due to binding to carbonic anhydrase. Brinzolamide is moderately bound (about 60%) to human plasma proteins.
Brimonidine exhibits affinity for pigmented ocular tissues, particularly iris-ciliary body, due to its known melanin binding properties. However, clinical and non-clinical safety data show it to be well-tolerated and safe during chronic administration.

Biotransformation
Brinzolamide is metabolized by hepatic cytochrome P450 isozymes, specifically CYP3A4, CYP2A6, CYP2B6, CYP2C8 and CYP2C9. The primary metabolite is N-desethylbrinzolamide followed by the N-desmethoxypropyl and O-desmethyl metabolites as well as an N-propionic acid analog formed by oxidation of the N-propyl sidechain of O-desmethyl brinzolamide. Brinzolamide and N-desethylbrinzolamide do not inhibit cytochrome P450 isozymes at concentrations at least 100-fold above maximum systemic levels.
Brimonidine is extensively metabolized by hepatic aldehyde oxidase with formation of 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine being the major metabolites. Oxidative cleavage of the imidazoline ring to 5-bromo-6-guanidinoquinoxaline is also observed.

Elimination
Brinzolamide is primarily eliminated in urineunchanged. In humans, urinary brinzolamide and N-desethylbrinzolamide accounted for about 60 and 6% of the dose, respectively. Data in rats showed some biliary excretion (about 30%), primarily as metabolites.

Brimonidine is primarily eliminated in the urine as metabolites. In rats and monkeys, urinary metabolites accounted for 60 to 75% of oral or intravenous doses

Linearity/non-linearity

Brinzolamide pharmacokinetics are inherently non-linear due to saturable binding to carbonic anhydrase in whole blood and various tissues. Steady-state exposure does not increase in a dose-proportional manner.

In contrast, brimonidine exhibits linear pharmacokinetics over the clinically therapeutic dose range.

Pharmacokinetic/pharmacodynamic relationship(s)

ZOLADIN is intended for local action within the eye. Assessment of human ocular exposure at efficacious doses is not feasible. The pharmacokinetic/pharmacodynamic relationship in humans for IOP-lowering has not been established.

Other special populations

Studies to determine the effects of age, race,and renal or hepatic impairment have not been conducted with ZOLADIN. A study of brinzolamide in Japanese versus non-Japanese subjects showed similar systemic pharmacokinetics between the two groups. In a study of brinzolamide in subjects with renal impairment, a 1.6-to 2.8-fold increase in the systemic exposure to brinzolamide and N-desethylbrinzolamide between normal and moderately renally-impaired subjects was demonstrated. This increase in steady-state RBC concentrations of substance-related material did not inhibit RBC carbonic anhydrase activity to levels that are associated with systemic side effects. However, the combination products not recommended for patientswith severe renal impairment (creatinine clearance < 30 mL/minute).

The Cmax, AUC and elimination half-life of brimonidine are similar in elderly (>65 years of age) subjects compared to young adults. The effects of renal and hepatic impairment on the systemic pharmacokinetics of brimonidine have not been evaluated. Given the low systemic exposure to brimonidine following topical ocular administration, it is expected that changes in plasma exposure would not be clinically relevant.

Paediatric population

The systemic pharmacokinetics of brinzolamide and brimonidine, alone or in combination, in paediatric patients have not been studied.

5.3 Preclinical Safety Data:

Brinzolamide

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

Effects in non-clinical reproduction and development toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. In rabbits, oral, maternally toxic, doses of brinzolamide of up to 6 mg/kg/day (261times the recommended daily clinical dose of 23µg/kg/day) revealed no effect on foetal development. In rats doses of 18 mg/kg/day (783 times the recommended daily clinical dose), but not 6 mg/kg/day, resulted in slightly reduced ossification of skull and sternebrae of foetuses. These findings were associated with 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 given 2 to 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

Brimonidine
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. Pharmaceutical Particulars :

6.1 List of excipients:

- Hydroxypropyl Methylcellulose (4000 cPs) (Methocel K4M CR Premium)
- Propylene Glycol
- Mannitol
- Tyloxapol
- Sodium Chloride
- Boric Acid
- Sodium Perborate
- Sodium Hydroxide
- Hydrochloric Acid
- Water for Injections

6.2 Incompatibilities:

None known.

6.3 Shelf life:

Two years from manufacture date.

6.4 Special precautions for storage:

- Store below 30°C and protect from light.
- Discard 30 days after opening.
- Keep out of the reach of children.

6.5 Nature and contents of container:

LDPE dropper bottle with LDPE tip and HDPE screw cap. Each box contains 1 labeled bottle with a folded package insert.

7. Marketing Authorization Holder :

Name	:	Aristopharma Ltd.
Principal office	:	7 Purana Paltan Line, Dhaka-1000, Bangladesh
Site of manufacturer	:	Plot # 14–22, Road # 11 & 12, Shampur-Kadamtali I/A, Dhaka-1204, Bangladesh
Telephone number	:	+880-2-9351691-93
Fax number	:	+880-2-8317005
e-mail	:	parvez@aristopharmabd.com

8. Marketing Authorization Numbers: 143–614–052

9. Date of first authorization / renewal of the authorization: - 19-03-2015

10. Date of revision of the text: - To be given after approval of the product.