Summary of Product Characteristics
(Product Data Sheet)

1.	**Name of the Medical Product** **Product Name: BRINZOX** (Brinzolamide Ophthalmic Suspension USP 1.0% w/v) **Pharmaceutical Dosage Form :** Ophthalmic Suspension (Eye Drops)
2.	**Qualitative & Quantitative Composition:** Brinzolamide USP 1.0% w/v Benzalkonium Chloride USPNF 0.01% w/v (As preservative) Sterile Aqueous base q.s.
3.	**Pharmaceutical Form:** Ophthalmic Suspension (Eye Drops) White to off-white coloured, aqueous suspension.
4. **4.1**	**Clinical Particulars** **Therapeutic Indications:** Brinzolamide is a carbonic anhydrase inhibitor indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.
4.2	**Dosage and Administration:** The recommended dose is one drop of Brinzolamide in the affected eye(s) 3 times daily. Brinzolamide may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.
4.3	**Contraindications:** Brinzolamide is contraindicated in patients who are hypersensitive to any component of this product.

4.4	**Warning and Precautions:** **Sulfonamide Hypersensitivity Reactions** Brinzolamide is a sulfonamide and although administered topically, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of Brinzolamide. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation. **Corneal Endothelium** Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing Brinzolamide to this group of patients. **Severe Renal Impairment** Brinzolamide has not been studied in patients with severe renal impairment [creatinine clearance (CrCl) less than 30 mL/min]. Because Brinzolamide and its metabolite are excreted predominantly by the kidney, Brinzolamide is not recommended in such patients. **Acute Angle-Closure Glaucoma** The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Brinzolamide has not been studied in patients with acute angle-closure glaucoma. **Risk of Contamination** Avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. **Contact Lens Wear** The preservative in Brinzolamide, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of Brinzolamide, but may be reinserted 15 minutes after instillation.

4.5	**Drug Interactions:** **Oral Carbonic Anhydrase Inhibitors** 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. The concomitant administration of Brinzolamide and oral carbonic anhydrase inhibitors is not recommended. **High-Dose Salicylate Therapy** Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving Brinzolamide.
4.6	**Pregnancy and Lactation:** **Pregnancy** There are no adequate and well-controlled studies in pregnant women to inform drug-associated risk. In reproductive toxicity studies, brinzolamide administered orally to rats induced fetal toxicity at 375-times the recommended human ophthalmic dose (RHOD) based on mg/kg. In rabbits, no fetal toxicity was observed following oral administration. **Lactation** There are no data on the presence of brinzolamide in human milk, the effects on the breastfed infant, or the effects on milk production. Brinzolamide has been detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for brinzolamide and any potential adverse effects on the breast-fed child from brinzolamide.
4.7	**Effects on ability to drive and use machine:** Brinzolamide has a 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. Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination.

4.8	**Adverse Reactions:** **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice. In clinical studies of Brinzolamide, the most frequently reported adverse reactions reported in 5% to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1% to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus, and rhinitis. The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing, and urticaria.
4.9	**Overdosage:** Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following oral administration of an overdose. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.
5.	**Clinical Pharmacology**
	Pharmacodynamic Properties: <u>Mechanism of Action</u> Carbonic anhydrase (CA) is an enzyme found in many tissues of the body, including the eye. Carbonic anhydrase catalyses 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, found primarily in red blood cells (RBCs), but also in other tissues. 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 IOP. Brinzox contains brinzolamide, an inhibitor of carbonic anhydrase II. Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated IOP. Elevated IOP is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

	Pharmacokinetics: Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for carbonic anhydrase II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to carbonic anhydrase and accumulates in RBCs. This metabolite binds mainly to carbonic anhydrase I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (less than 10 ng/mL). Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites. An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules of brinzolamide twice per day for up to 32 weeks. This regimen approximates the amount of drug delivered by topical ocular administration of brinzolamide dosed to both eyes 3 times per day and simulates systemic drug and metabolite concentrations similar to those achieved with long-term topical dosing. Red blood cell carbonic anhydrase activity was measured to assess the degree of systemic carbonic anhydrase inhibition. Brinzolamide saturation of RBC carbonic anhydrase II was achieved within 4 weeks (RBC concentrations of approximately 20 mcM). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20 to 28 weeks reaching concentrations ranging from 6 to 30 mcM. The inhibition of carbonic anhydrase II activity at steady state was approximately 70% to 75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.
	Preclinical Safety data: **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Brinzolamide caused urinary bladder tumors in female mice at oral doses of 10 mg/kg/day and in male rats at oral doses of 8 mg/kg/day in 2-year studies. Brinzolamide was not carcinogenic in male mice or female rats dosed orally for up to 2 years. The carcinogenicity appears secondary to kidney and urinary bladder toxicity. These levels of exposure cannot be achieved with topical ophthalmic dosing in humans. Mutagenesis The following tests for mutagenic potential were negative: (1) in vivo mouse micronucleus assay; (2) in vivo sister chromatid exchange assay; and (3) Ames E. coli test. The in vitro mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation.

	Impairment of Fertility In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the RHOD based on mg/kg).
6.	**Pharmaceutical particulars**
6.1	**List of Excipients:** Benzalkonium Chloride USPNF, Tyloxapol USP, Carbomer Homopolymer USPNF, Mannitol BP, Disodium Edetate BP, Sodium Chloride BP, Sodium Hydroxide BP, Water for Injection
6.2	**Incompatibilities:** Not applicable
6.3	**Shelf life:** 36 Months
6.4	**Special Precautions for storage:** Use the suspension within four weeks after first opening.
6.5	**Storage Condition:** Do not store above 30ºC.
6.6	**Nature and contents of container:** 5 mL vial packed in a carton along with pack insert.
7.	**Marketing Authorization Holder:** <u>Manufacturing Site :</u> Ajanta Pharma Ltd. Mirza - Palashbhari Road, Village Kokhjar, Kamrup (R), Guwahati, Assam – 781128 <u>Registered office:</u> Ajanta House, Charkop, Kandivli (W), Mumbai 400 067 India. **Marketing Authorization Numbers:** Not applicable.

8.	**Date of first authorization/ renewal of the authorization:** Not Applicable
9.	**Date of revision of text:** Dec 2021

BRINZOX Brinzolamide Ophthalmic Suspension USP 1 % w/v	
Module 1	Administrative Information and Product Information
Section 1.6	Product Information

1.6.2 Container labelling

Please find enclosed herewith artwork of Label.