NUBRIM-Z

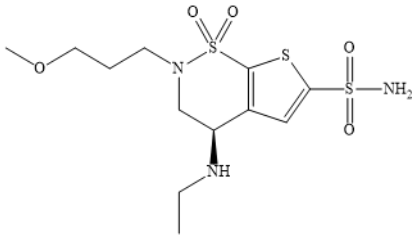
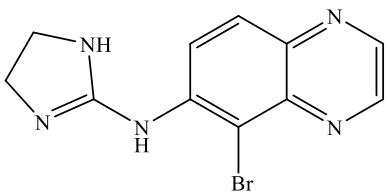
Brinzolamide 10mg, Brimonidine Tartrate e.q. to Brimonidine 2mg/ml Eye drop

--Benzalkonium chloride free

Nubrim-Z is an ophthalmic suspension of Brinzolamide (10 mg) and Brimonidine tartrate (e.q. to brimonidine 2mg/ml).

Brinzolamide is a carbonic anhydrase inhibitor used to lower intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (Iester, 2008). Brinzolamide is a white powder that cannot dissolve in water. It is commonly produced as a 1% ophthalmic suspension, which is used to lower IOP. The empirical formula of brinzolamide is $C_{12}H_{21}N_3O_5S_3$, and it has a melting point of around 131°C (**Table 1**). The effectiveness of brinzolamide at concentrations of 0.3% to 3% administered twice day has been assessed in multiple randomised double-blind, multicenter comparative clinical trials (March and Ochsner, 2000). Dose-response research was conducted to compare the effects of different concentrations of brinzolamide (0.3%, 1%, 2%, and 3%) on intraocular pressure (IOP). The study found that the mean reductions in IOP were 3 mmHg (11.3%), 4.3 mmHg (16.1%), 4.4 mmHg (16.1%), and 4.2 mmHg (15.4%) for the relevant doses. When measuring the intraocular pressure (IOP) during the day, it was found that brinzolamide 1% or 3% were more effective in considerably reducing IOP compared to brinzolamide 0.3% (Silver, 2000).

Table 1: The physical characteristics of Brinzolamide & Brimonidine tartrate.

S. No	**Physical characteristics**	**Brinzolamide**	**Brimonidine tartrate**
	Structure		

	Molecular weight	383.5 g/mol	442.22 g/mol
	Molecular formula	$C_{12}H_{21}N_3O_5S_3$	$C_{15}H_{16}BrN_5O_6$
	IUPAC Name	(4R)-4-(ethylamino)-2-(3-methoxypropyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide	5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)quinoxalin-6-amine;(2R,3R)-2,3-dihydroxybutanedioic acid
	Melting Point	131- 132 °C	252 °C
	Solubility	insoluble in water	Water soluble
	Type and mechanism	a sulfonamide and a thienothiazine | a selective carbonic anhydrase-II inhibitor	imidazole derivative | a selective alpha-2 adrenergic receptor agonist

Brinzolamide is a pharmacologically potent inhibitor of carbonic anhydrase II (CA-II), which effectively and reversibly suppresses the production of aqueous humour in the eye, leading to a drop in intraocular pressure (IOP) (Iester, 2008). It has the ability to catalyze the reversible formation of negatively charged bicarbonate ions from the interaction of water and carbon dioxide (CO_2) (**Figure 1**) (Lindskog, 1997). In order to produce pharmacological effects, nearly complete CA inhibition is necessary. Brinzolamide has half-lives of roughly three and five hours, respectively, before it is eliminated from the cornea and aqueous humour (Kadam et al., 2011). Thus, long after topical dosage, the cornea serves as a reservoir, delivering a steady flow of the medication to the ciliary processes of the ciliary body. There are seven distinct isoenzymatic forms in human tissues. CA-II is the most active isoenzymatic form and is mostly present in erythrocytes. Other organs that contain it include the kidneys, pancreas, eyes, central nervous system, and lungs. The pigment epithelium, corneal endothelial cells, and ciliary processes of the ciliary body are where the enzyme is mostly expressed in the eye (Aslam and Gupta, 2024; Stoner et al., 2022).

Several clinical trials (Zeyen and Caprioli 1993; Silver 1998; Sall 2000; Shin 2000; Wang et al 2004; Zhao and Chen 2005; Menon and Vernon 2006) have evaluated the safety of brinzolamide 1% ophthalmic suspension. The most commonly ocular adverse events were blurred vision (3%–8%), ocular discomfort (1.8%–5.9%), and eye pain (0.7%–4.0%). Other

ocular adverse events occurring at an incidence of less than 3% included hyperemia, pruritus, tearing, discharge, blepharitis, keratitis, foreign body sensation, dry eye, conjunctivitis, and lid margin crusting.

The safety of brinzolamide 1% ophthalmic suspension has been assessed in a number of clinical trials (Menon and Vernon, 2006; Sall, 2000; Wang et al., 2004, 2004; Zeyen and Caprioli, 1993; Zhao and Chen, 2005). Blurred vision (3%–8%), ocular discomfort (1.8%–5.9%), and eye pain (0.7%–4.0%) were the most frequent adverse effects related to the eyes. The following other ocular adverse effects had an incidence of less than 3%: blepharitis, keratitis, dry eye, conjunctivitis, hyperemia, pruritus, weeping, discharge, and lid edge crusting.

Brimonidine Tartrate is a water-soluble selective α2 adrenergic receptor agonist and the tartrate salt form of brimonidine, a quinoxaline derivative, a secondary amine, and a member of the imidazole family with the molecular formula $C_{15}H_{16}BrN_5O_6$ (**Table 1)**. It has been reported that brimonidine exhibits a selectivity of up to 1780-fold for α2-over-α1-adrenergic receptors. Brimonidine, when applied topically, decreases IOP within one hour. The maximum effect is observed 2-3 hours after administration. After dosage, the trough impact happens 10–14 hours later. Typically, a double daily dose of brimonidine is administered; no additional IOP lowering occurs at the morning trough when using tid versus bid dosing. Brimonidine lowers IOP through two different mechanisms: it decreases the formation of aqueous humour and increases its outflow through the uveoscleral route (**Figure 1**). Short-term brimonidine treatment mostly inhibits the formation of aqueous humour, but long-term treatment stimulates the outflow of aqueous humour via the uveoscleral route.

During the 1-year pivotal trials conducted for pharmacological approval, the use of brimonidine 0.2% twice daily resulted in a reduction of IOP that was comparable to or superior to timolol at its maximum impact (2 hours after administration). However, brimonidine 0.2% was less effective than timolol in reducing IOP during the morning trough period (Katz, 1999; LeBlanc, 1998; Schuman et al., 1997). The long-term effectiveness of brimonidine remained consistent, and after a duration of four years, brimonidine and timolol shown similar ability to lower intraocular pressure (IOP) at both the highest and lowest points of their effects (David, 2001). The pivotal trials demonstrated a high level of tolerance to Brimonidine. The medicine frequently caused side-effects such as dryness of the lips, redness of the eyes, and allergic reactions in the eyes. The incidence of treatment-induced ocular allergy to brimonidine over a one-year period was 11.5% (Katz, 1999). However, this rate may have been overestimated due to the misdiagnosis of dry eye, seasonal allergic conjunctivitis, or bacterial conjunctivitis as drug-related ocular allergy (Melamed and David, 2000).

Brinzolamide/brimonidine ophthalmic suspension has been proven effective in reducing increased intraocular pressure (IOP) in adult patients (aged > 18 years) with open-angle glaucoma or ocular hypertension. This conclusion was reached through four major, randomised, double-masked, phase III trials (Aung et al., 2014; Gandolfi et al., 2014; Katz et al., 2013; Nguyen et al., 2013).

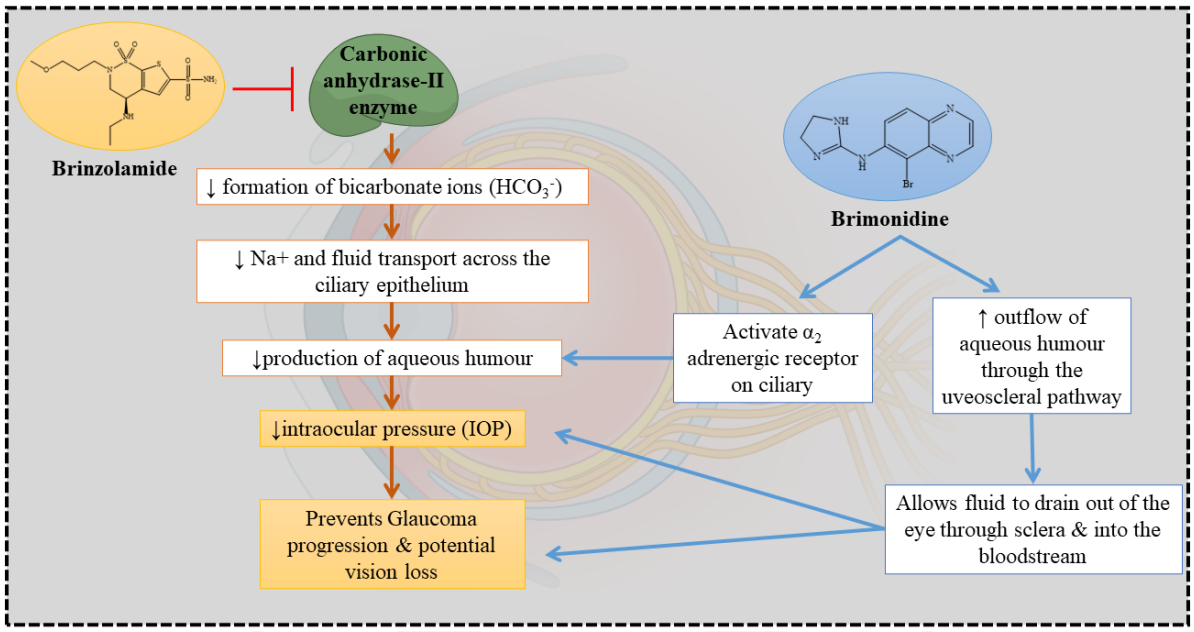


Figure 1: This figure illustrated the mechanism of action of Nubrim-Z Eye Drop. Nubrim-Z is an ocular suspension containing Brinzolamide (10 mg) and Brimonidine tartrate (equivalent to brimonidine 2 mg/ml). Brinzolamide exerts its antihypertensive activity by inhibiting the Carbonic anhydrase-II (CA-II) enzyme, which reduces the formation of bicarbonate ions, resulting in decreased transport of sodium (Na^+) ions and fluid across the ciliary, reducing the production of aqueous humour and lowering intraocular pressure (IOP), thereby preventing glaucoma progression and potential vision loss. Brimonidine reduces IOP through two pathways: by activating the α_2 adrenergic receptor, which decreases aqueous humour production; and by increasing the outflow of aqueous humour through the uveoscleral pathway, which allows fluid to drain out of the eye through the sclera and into the bloodstream, preventing glaucoma progression and vision loss.

Indications

- **Ocular Hypertension:** type of glaucoma where the fluid in the eye cannot drain properly, leading to pressure buildup and potential vision loss.

- **Open angle glaucoma:** a condition where the pressure inside the eye is higher than normal, but not high enough to be classified as glaucoma yet. Lowering eye pressure helps prevent future glaucoma development.

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