1. **Name of the Medicinal Product:**
   Brizagan (Brimonidine Tartrate 2mg/ml Eye drops Solution)

2. **Quality and Quantitative Composition :**

Ingredients	**Reference ***	**Qty/ ml (mg)**	**% composition (%w/v)**	**Function**
Brimonidine Tartrate	Ph.Eur c.ed.	2.00	0.2%	Drug substance
Benzalkonium Chloride	Ph.Eur c.ed.	0.05	0.005%	Preservative

For Excipeints refer Section 6.1.

* Whenever there is a change to the above mentioned Ph. Eur. monographs, it will be automatically adopted by the finished product manufacturer, without the need of submission of a variation application.

3. **Pharmaceutical form:**

Dosage form: Eye drop solution/Ophthalmic solution

Description: Clear, greenish-yellow to light greenish-yellow solution.

Route of administration: Ocular

Category: Prescription Only Medicines (POM)

4. Clinical Particulars:

4.1.Therapeutic indications:
Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.
- As monotherapy in patients in whom topical beta-blocker therapy is contraindicated.
- As adjunctive therapy to other intraocular pressure lowering medications when the target IOP is not achieved with a single agent.

4.2.Posology and method of administration:
Recommended dose in adults (including the elderly)
The recommended dose is one drop of Brizagan in the affected eye(s) twice daily, approximately 12 hours apart. No dosage adjustment is required for the use in elderly patients.
As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.
If more than one topical ophthalmic drug is to be used, the different drugs should be instilled 5-15 minutes apart.

Paediatric population
No clinical studies have been performed in adolescents (12 to 17 years).

Brimonidine is not recommended for use in children below 12 years and is contraindicated in neonates and infants (less than 2 years of age). It is known that severe adverse reactions can occur in neonates.
The safety and efficacy of brimonidine have not been established in children.

Special populations

Patients with hepatic and renal impairment

Brimonidine has not been studied in patients with hepatic or renal impairment.

Method of Administration

For ocular use

4.3.Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed.
- Neonates and infants.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

4.4.Special warning and precautions for use :

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤ 20 Kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease.

Some (12.7%) patients in clinical trials experienced an ocular allergic type reaction with brimonidine. If allergic reactions are observed, treatment with Brizagan should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine 0.2%, with some reported to be associated with an increase in IOP.

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

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

The preservative in Brizagan, benzalkonium chloride, may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.

Brizagan 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.

4.5.Interaction with other medicinal products and other forms of Interactions:

Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and miaserin).
Although specific drug interactions studies have not been conducted with brimonidine, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.
No data on the level of circulating catecholamines after brimonidine administration are available. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.
After the application of brimonidine, clinically insignificant decreases in blood pressure were noted in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with brimonidine.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

4.6.Pregnancy and lactation:

Pregnancy

The safety of use during human pregnancy has not been established. In animal studies, brimonidine tartrate did not cause any teratogenic effects. In rabbits, brimonidine tartrate, at plasma levels higher than are achieved during therapy in humans, has been shown to cause increased preimplantation loss and postnatal growth reduction. Brimonidine should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

It is not known if brimonidine is excreted in human milk. The compound is excreted in the milk of the lactating rat. Brimonidine should not be used by women nursing infants.

4.7.Effects on ability to drive and use machine:

Brimonidine may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery. Brimonidine may cause blurred and/or abnormal vision, which may impair the ability to drive or to use machinery, especially at night or in reduced lighting. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8.Adverse reactions :

The most commonly reported ADRs are oral dryness, ocular hyperaemia and burning/stinging, all occurring in 22 to 25% of patients. They are usually transient and not commonly of a severity requiring discontinuation of treatment.

Symptoms of ocular allergic reactions occurred in 12.7% of subjects (causing withdrawal in 11.5% of subjects) in clinical trials with the onset between 3 and 9 months in the majority of patients.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of undesirable effects: 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), not known (cannot be estimated from the available data); as presented in Table 1.

Table 1: Undesirable effects

System Organ Classification	Frequency	Adverse reaction
Cardiac disorders	Uncommon	palpitations/arrhythmias (including bradycardia and tachycardia)
Nervous system disorders	Very common	headache, drowsiness
	Common	dizziness, abnormal taste
	Very rare	syncope

Eye disorders	Very common	- ocular irritation (hyperaemia, burning and stinging, pruritus, foreign body sensation, conjunctival follicles); - blurred vision; - allergic blepharitis, allergic blepharoconjunctivitis, allergic conjunctivitis, ocular allergic reaction, and follicular conjunctivitis
	Common	- local irritation (eyelid hyperaemia and oedema, blepharitis, conjunctival oedema and discharge, ocular pain and tearing); - photophobia - corneal erosion and staining - ocular dryness - conjunctival blanching - abnormal vision - conjunctivitis
	Very rare	- iritis - miosis
Respiratory, thoracic and mediastinal disorders	Common	upper respiratory symptoms
	Uncommon	nasal dryness
	Rare	dyspnoea
Gastrointestinal disorders	Very common	oral dryness
	Common	gastrointestinal symptoms
Vascular disorders	Very rare	hypertension, hypotension
General disorders and administration site conditions	Very common	fatigue
	Common	asthenia
Immune system disorders	Uncommon	systemic allergic reactions
Psychiatric disorders	Uncommon	depression
	Very rare	insomnia

The following adverse reactions have been identified during post-marketing use of brimonidine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made:

Not known

Eye disorders:
- iridocyclitis (anterior uveitis)
- eyelid pruritus

Skin and subcutaneous tissue disorders:
- skin reaction including erythema, face oedema, pruritus, rash and vasodilatation

In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants receiving brimonidine.

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with brimonidine as adjunctive treatment. In 8% of children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-year-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing <20 kg (63%) compared to those weighing >20 kg (25%).

4.9.Overdose and special antidotes :

Ophthalmic overdose (Adults):
In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion (Adults):
There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension.

Treatment of oral overdose includes supportive and symptomatic therapy; patient's airways should be maintained.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population
Reports of serious adverse effects following inadvertent ingestion of brimonidine by paediatric subjects have been published. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6-24 hours.

5. Pharmacological Properties:

5.1.Pharmacodynamic Properties:

Pharmacotherapeutic group: Sympathomimetics in glaucoma therapy, ATC code = S01EA 05.

Mechanism of action

Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor.
This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.
Topical administration of brimonidine tartrate decreases intraocular pressure (IOP) in humans with minimal effect on cardiovascular or pulmonary parameters.
Limited data are available for patients with bronchial asthma showing no adverse effects.
Brimonidine has a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing. In two 1 year studies, brimonidine lowered IOP by mean values of approximately 4-6 mmHg.
Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. It is thought that brimonidine may lower IOP by reducing aqueous humour formation and enhancing uveoscleral outflow.

Clinical trials show that brimonidine is effective in combination with topical beta-blockers. Shorter term studies also suggest that brimonidine has a clinically relevant additive effect in combination with travoprost (6 weeks) and latanoprost (3 months).

5.2.Pharmacokinetic Properties:

a) General characteristics

After ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations were low (mean Cmax was 0.06 ng/ml). There was a slight accumulation in the blood after multiple (2 times daily for 10 days) instillations. The area under the plasma concentration-time curve over 12 hours at steady state (AUC0-12h) was 0.31 ng-hr/ml, as compared to 0.23 ng- hr/ mL after the first dose. The mean apparent half-life in the systemic circulation was approximately 3 hours in humans after topical dosing.

The plasma protein binding of brimonidine after topical dosing in humans is approximately 29%.

Brimonidine binds reversibly to melanin in ocular tissues, in vitro and in vivo. Following 2 weeks of ocular instillation, the concentrations of brimonidine in iris, ciliary body and choroid- retina were 3- to 17-fold higher than those after a single dose. Accumulation does not occur in the absence of melanin.

The significance of melanin binding in humans is unclear. However, no significant ocular adverse reaction was found during biomicroscopic examination of eyes in patients treated with brimonidine for up to one year, nor was significant ocular toxicity found during a one year ocular

safety study in monkeys given approximately four times the recommended dose of brimonidine tartrate.

Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 75% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Kinetics profile:

No great deviation from dose proportionality for plasma Cmax and AUC was observed following a single topical dose of 0.08%, 0.2% and 0.5%.
b) Characteristics in patients

Characteristics in elderly

patients:

The Cmax AUC, and apparent half-life of brimonidine are similar in the elderly (subjects 65 years or older) after a single dose compared with young adults, indicating that its systemic absorption and elimination are not affected by age.

Based on data from a 3 month clinical study, which included elderly patients, systemic exposure to brimonidine was very low.

5.3.Preclinical safety Data:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicty, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical Particulars:

6.1.List of excipients:
Benzalkonium Chloride , Polyvinyl alcohol, Sodium chloride , Sodium citrate Dihydrate, Citric acid monohydrate, Sodium hydroxide (for pH-adjustment), Hydrochloric acid (for pH-adjustment), Water for injection

6.2.**Incompatibilities:** None

6.3.Shelf life:
36 months
After first opening: Use within 28 days

6.4.Special precautions for storage:
Keep out of reach of children
Store below 30°C
After first opening of the bottle, to be kept for 28 days at temperature not exceeding 30°C

6.5.Nature and contents of container:
10ml bottle with dropper and cap in carton

6.6.Special precautions for disposal and other handling:
No special requirements

7. Marketing Authorization Holder and manufacturing site address:

Marketing Authorization Holder:
Mega Lifesciences Public Company Limited
384 Moo 4, Pattana 3 Road,
Bangpoo Industrial Estate,
Soi 6, Preaksa, Muang
Samutprakarn, Samutprakarn 10280,
Thailand

Manufacturing site address:
Rafarm SA
Thesi Pousi-Xatzi, Agiou Louka,
Paiania Attiki, 19002,
P.O. Box 37, Greece

8. Marketing Authorization Number

TAN 22 HM 0282

9. Date of first authorization / renewal of the authorization

19th June, 2022

10. Date of revision of the text