Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

COMBAT EYE DROP 5ML

2. Qualitative and quantitative composition

Each mL of COMBAT eye drops contains brimonidine tartrate 2.0 mg/mL and timolol (as maleate) 5.0 mg/Ml.

Excipients with known effect:
Contains benzalkonium chloride 0.05 mg/mL.
For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile ophthalmic solution

4. Clinical particulars

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

4.2 Posology and method of administration

To avoid contamination of the eye or eye drops do not allow the dropper tip to come into contact with any surface.
Posology
Recommended dosage in adults (including the elderly)

The recommended dose is one drop of Brimonidine Tartrate/Timolol in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

Method of administration

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctual occlusion) or eyelids are closed for two minutes. This should be performed immediately following the instillation of each drop. This may result in a decrease of systemic side effects and an increase in local activity.

Use in renal and hepatic impairment

Brimonidine Tartrate/Timolol has not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients.

Paediatric population:
Brimonidine Tartrate/Timolol is contraindicated in neonates and infants (less than 2 years of age) (see sections 4.3, 4.4, 4.8 and 4.9).
The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established and therefore, its use is not recommended in children or adolescents (see sections 4.4 and 4.8).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
• Reactive airway disease including bronchial asthma or a history of bronchial
• asthma, severe chronic obstructive pulmonary disease.
• Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree
• atrioventricular block not controlled with a pace-maker, overt cardiac failure,
• cardiogenic shock.
• Use in neonates and infants (less than 2 years of age) (see section 4.8)
• Patients receiving monoamine oxidase (MAO) inhibitor therapy.
• Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)

4.4 Special warnings and precautions for use

Paediatric population

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.
The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established (see sections 4.2 and 4.8).

Some patients have experienced ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) with brimonidine/timolol in clinical trials. Allergic conjunctivitis was seen in 5.2% of patients. Onset was typically between 3 and 9 months resulting in an overall discontinuation rate of 3.1%. Allergic blepharitis was uncommonly reported (<1%). If allergic reactions are observed, treatment with brimonidine/timolol should be discontinued.

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

Like other topically applied ophthalmic agents, brimonidine/timolol may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

Cardiac reactions have been reported including, rarely, death associated with cardiac failure following administration of timolol. 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, betablockers should only be given with caution to patients with first degree heart block.

As with systemic beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarct or sudden death.

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.

Respiratory disorders:

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta- blockers.

Brimonidine/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.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.
Brimonidine/timolol must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents

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 is not recommended (see section 4.5).

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 dose 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 anaesthetist must be informed if the patient is receiving timolol.

The preservative in Brimonidine Tartrate/Timolol, benzalkonium chloride, may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion.

Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses.
Brimonidine Tartrate/Timolol has not been studied in patients with closed-angle glaucoma.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with the brimonidine/timolol fixed combination. Although specific drug interactions studies have not been conducted with brimonidine/timolol, the theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, anti-arrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine. Also, after the application of brimonidine, very rare (<1 in 10,000) cases of hypotension have been reported. Caution is therefore advised when using brimonidine/timolol with systemic antihypertensives.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.
Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

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.

Concomitant use of a beta-blocker with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension (see section 4.4), and therefore the anaesthetist must be informed if the patient is using brimonidine/timolol.

Caution must be exercised if brimonidine/timolol is used concomitantly with iodine contrast products or intravenously administered lidocaine.
Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol.

No data on the level of circulating catecholamines after brimonidine tartrate/timolol administration are available. Caution, however, is

advised in patients taking medication which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

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).

Although specific drug interactions studies have not been conducted with brimonidine/timolol, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and mianserin), (see section 4.3). Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with brimonidine/timolol.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data for the use of the brimonidine timolol fixed combination in pregnant women. Brimonidine Tartrate/Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Brimonidine tartrate

There are no adequate data from the use of brimonidine tartrate in pregnant women. Studies in animals have shown reproductive toxicity at high maternotoxic doses (see section 5.3). The potential risk for humans is unknown.

Timolol

Studies in animals have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Epidemiological studies have not revealed malformative effects but have shown 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 brimonidine/timolol is

administered in pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Breastfeeding

Brimonidine tartrate

It is not known if brimonidine is excreted in human milk but it is excreted in the milk of the lactating rat.

Timolol

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.

Brimonidine Tartrate/Timolol should not be used by women breast-feeding infants.

4.7 Effects on ability to drive and use machines

Brimonidine/timolol has minor influence on the ability to drive and use machines. Brimonidine/timolol may cause transient blurring of vision, visual disturbance, fatigue and/or drowsiness which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared before driving or using machinery

4.8 Undesirable effects

Based on 12 month clinical trial data, the most commonly reported adverse drug reactions in the combination group were conjunctival hyperaemia (approximately 17% of patients) and burning sensation in the eye (approximately 11% of patients). The majority of cases were mild and led to discontinuation rates of only 3.4% and 0.5% respectively.

The most common adverse events in the brimonidine group were conjunctival hyperaemia (approximately 23% of patients), eye pruritus (approximately 12% of patients) and allergic conjunctivitis (approximately 10% of patients), leading to discontinuation in 8.9%, 4.5%, and 7.6% respectively. The most common adverse events in the timolol group were burning sensation in the eye (approximately 13% of patients) and conjunctival hyperaemia (approximately 8% of patients), leading to discontinuation in 1% and 0.5% respectively.

In the 12-month studies, discontinuations due to adverse events occurred in 14.3% of patients in the combination group compared with 30.6% in the brimonidine group and 5.1% in the timolol group.

Over 85% of patients in each treatment group showed no change in visual acuity, defined as less than a 2-line difference from baseline. An improvement in visual acuity of 2 lines or more was reported for 0.3% of patients in the combination group, and 0.1% each in the brimonidine and timolol groups. A worsening of visual acuity of 2 lines or more was reported for 9.4% of patients in the combination group, 9.2% in the brimonidine group, and 12.2% of patients in the timolol group.

Overall, approximately 95% of patients in each treatment group showed a <5 dB change in mean deviation of the visual fields from baseline. Improvement in visual fields (increase of >5 dB) was reported for 0.9% of patients in the timolol group, 0.6% in the combination group, and 0% in the brimonidine group. Worsening of visual fields of ≥ 5dB was reported for 3.4% of patients in the combination group, 4.6% of patients in the brimonidine group, and 3.4% of patients in the timolol group.

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

Rare reports of overdosage with brimonidine/timolol in humans resulted in no adverse outcome. Treatment of an overdose includes supportive and symptomatic therapy; a patient's airway should be maintained.

Brimonidine tartrate

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 or reported. 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.

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness and cardiac arrest. A study of patients showed that timolol did not dialyse readily.

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

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%.

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), Purified water

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 Content 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

Marketing Authorization Holder:
Mega Lifesciences Public Company Limited
384 Moo 4, Pattana 3 Road,
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8. Marketing Authorization Number

CTD11616

9. Date of first authorization/renewal of the authorization

09/07/2024

10. Date of revision of the text

12/5/2025