SCHEDULING STATUS

S3

1. NAME OF MEDICINE

COMBIGAN 2 mg/ml + 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains:

2,0 mg brimonidine tartrate equivalent to 1,3 mg brimonidine

5,0 mg timolol as 6,8 mg timolol maleate.

Excipients with known effect

Contains benzalkonium chloride 0,05 mg/ml

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, greenish-yellow to light greenish-yellow solution, essentially free from particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Control of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are stabilised on the individual components given at the same dosages.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including the elderly)

The recommended dose is one drop of COMBIGAN in the affected eye(s) twice daily, approximately 12 hours apart.

Special populations

Use in renal and hepatic impairment

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

Paediatric population

Safety and efficacy have not been demonstrated in patients younger than 18 years (see section 4.3).

Method of administration

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.

To avoid contamination of the eye or eye drops do not allow the dropper tip to come into contact with any surface. Keep the container tightly closed.

If more than one topical ophthalmic medicine is to be used, the different medicines should be instilled at least 5 minutes apart.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- The safety and effectiveness in patients less than 18 years of age have not been established (see section 4.4).
- Reactive airway disease including bronchospasm, bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease (see section 4.4).
- Sinus bradycardia, sick sinus syndrome, sino-atrial nodal block, second and third degree atrioventricular block not controlled with a pacemaker, overt cardiac failure (see section 4.4), cardiogenic shock.
- Use in neonates and infants (less than two years of age) (see section 4.4, Paediatric population).
- Patients receiving monoamine oxidase (MAO) inhibitor therapy or within 2 weeks of stopping MAO-inhibitor therapy.
- Concomitant use of linezolid.
- Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants).

4.4 Special warnings and precautions for use

Respiratory and cardiac reactions have been reported including death due to bronchospasm or associated with cardiac failure.

Hypersensitivity: Because of the brimonidine tartrate component COMBIGAN should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists. 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 accidental, diagnostic, or therapeutic challenge with such allergens. These patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions since

timolol maleate may blunt the beta-agonist effect of epinephrine (adrenaline). In such cases, alternatives to epinephrine should be considered.

Allergic conjunctivitis was seen in 5,2 % of patients using COMBIGAN in clinical trials. 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 COMBIGAN 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.

COMBIGAN 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 medicines may occur. To reduce the systemic absorption, see section 4.2, Method of administration.

General: Patients prescribed IOP-lowering medication should be routinely monitored for IOP. COMBIGAN ophthalmic solution should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension or thromboangitis obliterans.

Cardiac disorders: 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 monitored for signs of deterioration of these diseases and of adverse reactions. Due to its negative effect on conduction time, beta-

blockers should only be given with caution to patients with first degree heart block.

COMBIGAN may enhance the hypotensive effects of all types of anti-hypertensives (see section 4.5).

Vascular disorders: Patients with severe peripheral circulatory disturbance/disorders (i.e. Raynaud's phenomenon) should be treated with caution.

Respiratory disorders: Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of ophthalmic beta-blockers, such as in COMBIGAN. COMBIGAN should be used with caution, in patients with mild/moderate asthma and only if the potential benefit outweighs the potential risk (see section 4.3).

Obstructive pulmonary disease: Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma in which COMBIGAN is contraindicated) should not receive beta-blocking medicines, including COMBIGAN.

Hypoglycaemia / Diabetes: Beta-blockers such as those contained in COMBIGAN should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with diabetes mellitus (especially those with labile diabetes) as beta-blockers such as those contained in COMBIGAN may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism and thyrotoxicosis: Beta-blockers as contained in COMBIGAN may mask the signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing

thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking medicines that might precipitate a thyroid storm.

COMBIGAN must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

Corneal diseases: Ophthalmic beta-blockers such as in COMBIGAN may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking medicines: Caution should be exercised when used concomitantly with systemic beta-adrenergic blocking medicines because of the potential for additive effects on systemic beta-blockade. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended (see section 4.5).

Choroidal detachment: Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol as in COMBIGAN) after filtration procedures.

Major surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking medication including COMBIGAN prior to major surgery is controversial. If necessary, during surgery, the effects of beta-adrenergic blocking medicines may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Surgical anaesthesia: Beta-blocking ophthalmological preparations such as in COMBIGAN may block systemic beta-agonist effects e.g. of adrenaline. COMBIGAN may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anaesthetics. The anaesthetist must be informed if the patient is using COMBIGAN.

Angle-closure glaucoma: COMBIGAN has not been studied in patients with closed-angle glaucoma.

Muscle weakness: Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness). Timolol maleate, as contained in COMBIGAN, has been reported to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Cerebrovascular insufficiency: Because of potential effects of beta-adrenergic blocking medicines on blood pressure and pulse, COMBIGAN should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with COMBIGAN, alternative therapy should be considered.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations such as COMBIGAN cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication such as COMBIGAN over an extended period in patients with extensive ocular surface disease.

Information for patients: Patients should be instructed to avoid allowing the tip of the dispensing container to make contact with the eye or surrounding structures. If handled improperly, COMBIGAN 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 COMBIGAN.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic medicines, including COMBIGAN. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption to the ocular epithelial surface.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g. trauma or infection), they should immediately seek their doctor's advice concerning the continued use of the present multi-dose container.

Contact lenses: The preservative in COMBIGAN, benzalkonium chloride, may cause eye irritation. Patients wearing contact lenses should be instructed to remove them prior to application and wait at least 15 minutes after instilling COMBIGAN before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

Paediatric population

The use of COMBIGAN in paediatric patients is not recommended. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0,2 % to infants in the age range of 28 days to 3 months. COMBIGAN should not be used in patients younger than 18 years of age.

There are no adequate and well-controlled studies with COMBIGAN in children less than 18 years old. In a 3-month, Phase 3 study in children (ages 2-7 years) with glaucoma inadequately controlled by beta-blockers, a high prevalence of somnolence (55 %) was reported with brimonidine tartrate ophthalmic solution 0,2 % as adjunctive treatment to topical beta-blockers. Somnolence was severe in 8 % of the children and led to discontinuation of treatment in 13 %.

During post-marketing surveillance, apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving brimonidine either for congenital glaucoma or by accidental ingestion (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with COMBIGAN.

Monoamine oxidase (MAO) inhibitor therapy: Brimonidine is contraindicated in patients receiving monoamine oxidase inhibitor (MAOI) therapy, including the antibiotic linezolid, and in patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and miaserin) (see section 4.3). Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with COMBIGAN.

CNS depressants: No interaction studies have been performed with COMBIGAN. The theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

Beta-adrenergic blocking medicines: Patients who are receiving both a systemic (e.g., oral or intravenous) beta-adrenergic blocking medicine and COMBIGAN should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure (see section 4.4).

Anti-hypertensives / Digoxin: 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 medicines, anti-dysrhythmics (including amiodarone), digoxin or parasympathomimetics.

Epinephrine: Mydriasis resulting from concomitant use of timolol maleate, an ingredient in COMBIGAN and adrenaline (epinephrine) has been reported. COMBIGAN may increase the hypoglycaemic effect of antidiabetic medicines. COMBIGAN can mask the signs and symptoms of hypoglycaemia (see section 4.4).

Clonidine: The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers such as COMBIGAN.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxeteine, paroxetine) and timolol, an ingredient of COMBIGAN.

Concomitant use of timolol as in COMBIGAN with anaesthetic medicines 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 COMBIGAN.

Iodine contrast products / Lidocaine (lignocaine): Caution must be exercised if COMBIGAN is used concomitantly with iodine contrast products or intravenously administered lidocaine (lignocaine).

Cimetidine / Hydralazine / Alcohol: Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol.

Calcium channel blockers or catecholamine-depleting agents: No data on the level of

circulating catecholamines after COMBIGAN 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).

Alpha-adrenergic agonists: Caution is advised when initiating (or changing the dose of) a concomitant systemic medicine (irrespective of pharmaceutical form) which may interact with alpha-adrenergic agonists or interfere with their activity (i.e. agonists or antagonists of the adrenergic receptor such as isoprenaline or prazosin).

Prostamides / Prostaglandins / Carbonic anhydrase inhibitors / Pilocarpine: Although specific medicine interactions studies have not been conducted with COMBIGAN, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

4.6 Fertility, pregnancy and lactation

Safety of COMBIGAN in pregnancy and lactation has not been established in controlled clinical studies in pregnant or lactating women.

Pregnancy

Brimonidine tartrate

Studies in rats have shown reproductive toxicity only at high maternotoxic doses representing an exposure margin 580-times the human exposure after topical ocular COMBIGAN. There was no reproductive toxicity observed in rabbits. 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. No foetal malformations were observed in mice, rats or rabbits at

oral doses up to 50 mg/kg/day which is 4200-fold the daily dose of COMBIGAN in humans. However, epidemiological studies suggest that a risk of intra uterine growth retardation may exist following exposure to systemic beta-blockers. In addition, some signs and symptoms of beta-blockade (e.g. bradycardia) have been observed in both the foetus and the neonate. Consequently, COMBIGAN should not be used during pregnancy.

Breastfeeding

COMBIGAN should not be used by women breast-feeding infants.

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.

4.7 Effects on ability to drive and use machines

COMBIGAN may influence the ability to drive and use machines. COMBIGAN 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

Summary of the safety profile

The most commonly reported side effects are conjunctival hyperaemia (approximately 15 % of patients) and burning sensation in the eye (approximately 11 % of patients). The majority of these cases were mild and led to discontinuation rates of only 3,4 % and 0,5 % respectively.

Tabulated list of adverse reactions

The frequency of adverse reactions documented during clinical trials and through post-marketing experience is given below and is defined as follows: 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 available data).

System organ class	Frequency	Adverse Reaction / Side Effect
Eye disorders	Very common	Conjunctival hyperaemia, burning sensation
	Common	Stinging sensation in the eye, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, corneal erosion, superficial punctuate keratitis, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation, eyelid erythema, eyelids pruritus, eyelid oedema
	Uncommon	Visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment
	Not known	Vision blurred, reduced visual acuity
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Somnolence, headache, dizziness
	Uncommon	Syncope

Cardiac disorders	Common	Bradycardia
	Uncommon	Congestive heart failure, palpitations
	Not known	Dysrhythmia, bradycardia, tachycardia
Vascular disorders	Common	Hypertension
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis
	Uncommon	Nasal dryness
Gastrointestinal disorders	Common	Oral dryness, nausea, diarrhoea
	Uncommon	Taste perversion
Immune system disorders	Uncommon	Allergic contact dermatitis
Skin and subcutaneous disorders	Not known	Facial erythema
General disorders and administration site conditions	Common	Asthenia

Brimonidine

System organ class	**Adverse Reaction / Side Effect**
Eye disorders	Iritis, iridocyclitis (anterior uveitis), miosis
Psychiatric disorders	Insomnia
Respiratory, thoracic and mediastinal disorders	Upper respiratory symptoms, dyspnoea
Gastrointestinal disorders	Gastrointestinal symptoms
General disorders and administration site conditions	Systemic allergic reactions
Immune system disorders	Hypersensitivity, skin reaction including erythema, face oedema, pruritus, rash and vasodilatation

A high incidence and severity of somnolence has been reported in children of 2 years of age and older, especially those in the 2-7 age range and/or weighing ≤ 20 kg (see section 4.3 and 4.4).

Timolol

COMBIGAN (brimonidine tartrate / timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking medicines.

To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with COMBIGAN are listed below.

System organ class	**Adverse Reaction / Side Effect**
Immune system disorders	Systemic allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash, pruritus, systemic lupus erythematosus
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Behavioural changes and psychic disturbances including anxiety, confusion, disorientation, hallucinations, insomnia, nightmares, memory loss, nervousness
Nervous system disorders	Cerebral vascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, paraesthesia
Eye disorders	Keratitis, decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery (see section

	4.4), corneal erosion, cystoid macular oedema, pseudopemphigoid, refractive changes
Cardiac disorders	Chest pain, oedema, atrioventricular block, cardiac arrest, cardiac failure, heart block, pulmonary oedema, worsening of angina pectoris
Ear and labyrinth disorders	Tinnitus
Vascular disorders	Raynaud's phenomenon, cold hands and feet, claudication
Respiratory, thoracic and mediastinal disorders	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough, nasal congestion, respiratory failure, upper respiratory infection
Gastrointestinal disorders	Dyspepsia, abdominal pain, vomiting, anorexia, dysgeusia
Skin and subcutaneous tissue disorders	Alopecia, psoriasiform rash, exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders	Myalgia
Reproductive system and breast disorders	Sexual dysfunction, decreased libido, Peyronie's disease, retroperitoneal fibrosis
General disorders and administration site conditions	Fatigue

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

You can also report side effects to AbbVie (Pty) Ltd by sending an email to MEAPV@abbvie.com.

4.9 Overdose

There is limited data available of overdosage in humans with the use of COMBIGAN. Bradycardia has been reported in association with use of a higher than recommended dose. If overdosage occurs, treatment should be symptomatic and supportive. A patent airway should be maintained.

Brimonidine

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.

Paediatric population

Symptoms of brimonidine overdose such as apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving brimonidine tartrate ophthalmic solution as part of medical treatment of congenital glaucoma or by accidental oral ingestion (see section 4.4, Paediatric population).

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

Pharmacological classification: A. 15.4 Ophthalmic preparations. Others.

The combination of brimonidine tartrate and timolol maleate in an ophthalmic solution reduces intraocular pressure (IOP) by reducing aqueous humour production and increasing uveoscleral outflow.

Brimonidine tartrate is an alpha$_2$ adrenergic receptor agonist.

It is thought that brimonidine tartrate lowers IOP by reducing aqueous humour production and increasing uveoscleral outflow.

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that combines reversibly with the beta-adrenergic receptor. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not yet clearly established.

5.2 Pharmacokinetic properties

Plasma brimonidine tartrate and timolol maleate concentrations were determined in healthy subjects and patients following topical dosing with the combination ophthalmic solution. Normal volunteers dosed with one drop of the combination ophthalmic solution twice daily in both eyes for seven days showed peak plasma brimonidine and timolol concentration of 0,03 ng/ml and 0,4 ng/ml, respectively. Plasma concentrations of brimonidine peaked within 1 to 4 hours after ocular dosing and declined with a systemic half-life of approximately 3 hours. Peak plasma concentrations of timolol occurred in about 1 to 3 hours post-dose. The apparent systemic half-life of timolol was about 7 hours after ocular administration.

In a crossover study with the combination ophthalmic solution in healthy volunteers, there were no significant differences in brimonidine or timolol area under the plasma concentration time curve between the combination ophthalmic solution and the respective monotherapy treatments.

In two Phase 3 trials, brimonidine tartrate and timolol maleate plasma concentrations from the combination ophthalmic solution BID treatment group were 15 – 49 % lower than their respective monotherapy values. The lower plasma brimonidine tartrate concentration with the combination ophthalmic solution appears to be due to twice-daily dosing for the combination ophthalmic solution versus three-times dosing with brimonidine tartrate 0,2 % (ALPHAGAN). The lower timolol maleate plasma concentrations seen with the combination ophthalmic solution, as compared to timolol maleate 0,5 %, appear to be related to a slower absorption of timolol maleate, which may be due to a difference in the benzalkonium concentrations rather than a medicine-medicine (brimonidine tartrate - timolol maleate) interaction.

In humans, systemic metabolism of brimonidine is extensive. It is metabolised primarily by the liver and there is no marked systemic accumulation after multiple dosing. Urinary excretion is the major route of elimination of the medicine and its metabolites. Approximately 87 % of an orally-administration radioactive dose was eliminated within 120 hours, with 74 % found in the urine.

Orally administered timolol maleate is nearly completely absorbed (~90 % availability). The apparent elimination half-life of timolol maleate in plasma is 4 hours.

Timolol maleate is partially metabolised by the liver. After oral dosing, timolol maleate is subject to moderate first-pass metabolism (~50 %). Urinary excretion is the major route of elimination of timolol maleate and its metabolites. Only a small amount of unchanged medicine

appears in the urine, along with its metabolites after oral dosing.

Both brimonidine and timolol are not extensively bound to plasma proteins. Brimonidine binds ~29 % and timolol is ~60 % bound to plasma proteins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Sodium phosphate, monobasic monohydrate

Sodium phosphate, dibasic heptahydrate

Hydrochloric acid or sodium hydroxide to adjust pH

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

After first opening: Use within 30 days

6.4 Special precautions for storage

Store at or below 25 °C, protected from light. Do not refrigerate.

6.5 Nature and contents of container

White, opaque LDPE bottles with polystyrene caps. Each bottle has a fill volume of 5 ml, 10 ml or 15 ml.

The following pack sizes are available: cartons containing 1 bottle of 5 ml, 10 ml or 15 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Building 7, Waterfall Corporate Campus

74 Waterfall Drive

Waterfall City

Midrand, 1685

South Africa

8. REGISTRATION NUMBER

A39/15.4/0464

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

30 November 2007

10. DATE OF REVISION OF TEXT

17 February 2025

CCDS v3.1, UK SmPC 24/11/2020