NEW ZEALAND DATA SHEET

1. PRODUCT NAME

COMBIGAN® brimonidine tartrate 0.2% and timolol (as maleate) 0.5% eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of COMBIGAN® eye drops contains brimonidine tartrate 2.0 mg/mL and timolol (as maleate) 5.0 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

COMBIGAN® eye drops are indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension not adequately responding to monotherapy.

4.2 Dosage and method of administration

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

In order to minimise systemic absorption of COMBIGAN® eye drops, apply pressure to the tear duct immediately following administration of the drug.

As with all eye drops containing benzalkonium chloride as a preservative, there is potential for incompatibility with other topical ophthalmic medications. If more than one topical ophthalmic drug is to be used, other eye drops should not be used within five to ten minutes of using COMBIGAN® eye drops.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established. During post-marketing surveillance, apnea, 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 also Contraindications.

Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and other adult patients. In a brimonidine only study evaluating the accumulation of brimonidine tartrate in plasma following dosing of brimonidine tartrate alone, the Cmax and apparent half-life of brimonidine were similar in elderly subjects (65 years or older) and younger adults, indicating that its systemic absorption and elimination were not significantly affected by age.

4.3 Contraindications

COMBIGAN® eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate, timolol maleate or any of the excipients listed in section 6.1. In patients receiving monoamine oxidase (MAO) inhibitor therapy, in patients with bronchospasm, bronchial asthma or patients with a history of bronchial asthma, or severe chronic obstructive pulmonary disease, in patients with sinus bradycardia, sick sinus syndrome, sinoatrial nodal block, second or third degree atrioventricular block not controlled with a pacemaker, overt cardiac failure or cardiogenic shock.

Patients who have been receiving MAO inhibitor therapy should wait 14 days after discontinuation before commencing therapy.

COMBIGAN® eye drops are also contraindicated in neonates and infants, ie children under the age of 2 years.

4.4 Special warnings and precautions for use

General

Like other topically applied ophthalmic agents, COMBIGAN® may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed.

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension. Cardiac failure should be adequately controlled before beginning therapy. Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At first sign or symptom of cardiac failure, COMBIGAN® should be discontinued. Cardiac and respiratory reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failure have been reported following administration of timolol maleate.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Children 2 years of age and above, especially those weighing ≤ 20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence.

COMBIGAN® eye drops have not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients. In patients with severe renal impairment on dialysis, treatment with timolol has been associated with pronounced hypotension.

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

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection) or any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their doctor's advice concerning the continued use of the product.

Beta-blockers may also mask the clinical signs of hyperthyroidism (e.g. tachycardia) and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Patients who are already receiving a beta-adrenergic blocking agent orally and who are given timolol should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

COMBIGAN® should not be used alone in the treatment of acute angle-closure glaucoma.

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

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedure.

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 and may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents as beta-blockers may mask the signs and symptoms (e.g. tachycardia) of acute hypoglycaemia.

Beta-adrenergic receptor blockade impairs the ability of the heart to respond to betaadrenergically mediated reflex stimuli. This may augment the risk of general anaesthesia in surgical procedures. In patients undergoing elective surgery, it may be necessary to gradually withdraw the beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

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

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents 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®, alternate therapy should be considered.

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 timolol is contraindicated [see Contraindications]) should, in general, not receive products containing beta-blockers, including COMBIGAN® however, if COMBIGAN® is deemed necessary in such patients, it should be administered with caution

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.

Preclinical Findings

Carcinogenicity, Mutagenicity and Impairment of Fertility

No study has been conducted to investigate the carcinogenicity, mutagenicity or effects on fertility of COMBIGAN®. The following information is based on studies with timolol maleate or brimonidine tartrate alone.

In a two-year study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats dosed orally at 300 mg/kg/day, but not at 100 mg/kg/day (approximately 1000 times the maximum recommended ophthalmic dose in humans on a “mg/m^2” basis). In a long-term study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas in female mice dosed orally at 500 mg/kg/day, but not at 50 mg/kg/day (approximately 300 times the maximum recommended ophthalmic dose in humans on a “mg/m^2” basis). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas in female mice was associated with elevations in serum prolactin. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established

in humans. In adult women who received oral treatment with timolol maleate at doses up to 60 mg (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

No compound-related carcinogenic effects of brimonidine were observed in a 21-month study in mice or a 2-year study in rats at oral doses up to 2.5 and 1 mg/kg/day (as the free base), respectively, with plasma concentrations of brimonidine at least 150 times those expected in humans dosed therapeutically.

Both in vitro and in vivo studies (Ames test, neoplastic cell transformation assay, cytogenetic assay and micronucleus test in mice) showed no genotoxicity of timolol. Negative results were also observed for brimonidine in assays for chromosomal damage (Chinese hamster cells in vitro, in vivo bone marrow cytogenetic assay and a dominant lethal assay). In gene mutation assays with S. typhimurium and E. coli, brimonidine gave a positive response in one S. typhimurium strain without metabolic activation but gave negative results in other tester strains.

Reproductive toxicity studies of timolol in rats showed no adverse effects on male or female fertility at oral doses up to 100 mg/kg/day. A study of brimonidine in rats also did not reveal significant effects on fertility at oral doses of up to 0.66 mg/kg/day.

The preservative in COMBIGAN® eye drops, benzalkonium chloride, may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft contact lenses should be instructed to remove contact lenses prior to administration of the solution and wait at least 15 minutes after using COMBIGAN® eye drops before reinserting soft contact lenses.

Patients should be instructed that allowing the tip of the dispensing container to contact the eye or surrounding structures can cause injury and/or contamination of eye drops. Serious damage to the eye and subsequent loss of vision may result from using contaminated solution.

4.5 Interactions with other medicines and other forms of interaction

Although specific drug interaction studies have not been conducted with COMBIGAN® eye drops, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. There is potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops with timolol are administered concomitantly with guanethidine, anti-arrhythmics, or parasympathomimetics.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as COMBIGAN®, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Patients who are receiving a beta-adrenergic blocking agent orally and COMBIGAN® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure.

Because COMBIGAN® may reduce blood pressure, caution in using concomitant drugs such as anti-hypertensives and/or cardiac glycosides is advised.

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).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. It is not known whether the concurrent use of these agents with COMBIGAN® in humans can lead to resulting interference with IOP lowering effects. No data on the level of circulating catecholamines after COMBIGAN® eye drops are instilled are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

As brimonidine tartrate is metabolised primarily by the liver, most likely by cytochrome P450 and aldehyde oxidase, COMBIGAN® eye drops may affect the metabolism of other drugs that utilise the cytochrome P450 pathway.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CY2D6 inhibitors (e.g. quinidine, selective serotonin reuptake inhibitors) and timolol, possibly because quinidine inhibits the metabolism of timolol via the P450 enzyme, CYP2D6.

Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Concomitant use of a beta blocker with aesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension. The anaesthetist must therefore be informed if the patient is taking COMBIGAN®.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Category C

There are no adequate data on the use of COMBIGAN® eye drops in pregnant women.

Timolol was not teratogenic in mice, rats or rabbits at oral doses up to 50 mg/kg/day (over 300 times the maximum recommended clinical dose on a “mg/m^2” basis), although delayed fetal ossification was observed at this dose in rats. There were no adverse effects on postnatal development of offspring. At higher doses, there were increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) in mice (1000 mg/kg/day), increased resorptions in rabbits (≥ 90 mg/kg/day), and a decreased number

of caudal vertebral bodies and arches as well as an increase in hypoplastic sternebrae in rats (500 mg/kg/day).

Epidemiological studies suggest that owing to their pharmacological effects beta-blockers may reduce placental perfusion, which may result in intrauterine growth retardation, premature delivery, or fetal death. In addition, undesirable effects (e.g. bradycardia and hypoglycaemia) may occur in the foetus and the neonate. There is also an increased risk of cardiac and pulmonary complications in a neonate that has been exposed to a beta-blocker.

Brimonidine was not teratogenic in rats or rabbits. However, the drug crosses the placenta and enters fetal circulation in rats. At exposures of about 580 times that maximally anticipated in humans (based on AUC), brimonidine was associated with both maternal and embryofetal toxicity (increased early resorptions/post-implantation losses and decreased pup viability and body weights) in rats. Brimonidine was predominant in the placenta, uterus and fetal liver but not in maternal liver. Evidence for maternal and embryofetal toxicity (abortions) of brimonidine was also observed in rabbits at exposures about 37 times that maximally anticipated in humans.

Because animal reproduction studies are not always predictive of human responses, COMBIGAN® should not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether brimonidine is excreted in human milk. In lactating rats, levels of the drug in milk were up to 12 times higher than those in maternal plasma; and in a peri- and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 55 times greater than those expected in humans.

Timolol is excreted in human milk following oral and ophthalmic administration and there is potential for serious adverse reactions from timolol in breastfed infants.

Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue COMBIGAN® eye drops, taking into account the importance of COMBIGAN® eye drops to the mother.

4.7 Effects on ability to drive and use machines

As with other similar medications, COMBIGAN® eye drops can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities requiring mental alertness, including driving and operating machinery, should be cautioned of the potential for a decrease in mental alertness. COMBIGAN® may also cause transient blurred vision or visual disturbances. 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 ≥ 5 dB 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.

Greater than 96% of patients in each treatment group showed a minimal change (between >-0.2 and < +0.2) from baseline in Cup/Disc ratio. Worsening of ≥ +0.2 was reported for 2.1% of patients in the combination group, 0.8% of patients in the brimonidine group, and 2.1% of patients in the timolol group.

The following adverse drug reactions were reported during clinical trials with COMBIGAN® eye drops:

Eye disorders:

Very common (>1/10): conjunctival hyperaemia, burning sensation.

Common (>1/100, <1/10): stinging sensation in the eye, eye pruritus, eyelid oedema, eyelid pruritus, eyelid erythema, allergic conjunctivitis, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, corneal erosion, superficial punctate keratitis, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation.

Uncommon (>1/1000, <1/100): visual acuity worsened, conjunctival oedema, follicular conjunctivitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, abnormal vision, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment.

Psychiatric disorders:

Common (>1/100, <1/10): depression

Nervous system disorders:

Common (>1/100, <1/10): somnolence, headache

Uncommon (>1/1000, <1/100): dizziness, syncope

Cardiac disorders:

Uncommon (>1/1000, <1/100): congestive heart failure, palpitations, bradycardia

Vascular disorders:

Common (>1/100, <1/10): hypertension

Uncommon (>1/1000, <1/100): hypotension

Respiratory, thoracic and mediastinal disorders:

Uncommon (>1/1000, <1/100): rhinitis, nasal dryness

Gastrointestinal disorders:

Common (>1/100, <1/10): oral dryness

Uncommon (>1/1000, <1/100): taste perversion, diarrhoea, nausea

Immune system disorders:

Uncommon (>1/1000, <1/100): allergic contact dermatitis

General disorders and administration site conditions:

Common (>1/100, <1/10): asthenic conditions

Investigations:

Common (>1/100, <1/10): LFTs abnormal

Additional adverse events that have been seen with one of the components and may potentially occur also with COMBIGAN® eye drops are as follows:

Brimonidine tartrate

Eye Disorders:

Blurring, ocular allergic reaction, corneal staining, conjunctival discharge and conjunctival papillae, iritis, iridocyclitis (anterior uveitis), miosis.

Immune system disorders:

Hypersensitivity, skin reaction (including erythema, face oedema, pruritus, rash); vasodilation.

Psychiatric disorders: Insomnia

*Cardiac disorders: Palpitations/*arrhythmias, tachycardia

Vascular disorders: Syncope

Respiratory, thoracic and mediastinal disorders: Upper respiratory symptoms, nasal dryness

Gastrointestinal disorders: Gastrointestinal symptoms, taste perversion

Systemic effects: Fatigue/drowsiness and systemic allergic reaction.

Timolol

Immune system disorders:

Signs and symptoms of systemic allergic reactions, including anaphylaxis, angiooedema, pruritus, uticaria, and generalised and localized rash, systemic lupus erythematosus.

Endocrine disorders:

Masked symptoms of hypoglycaemia in diabetes patients (see Warnings and Precautions)

Nervous system/Psychiatric disorders:

Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, memory loss, fatigue and paraesthesia.

Eye disorders:

Choroidal detachment following filtration surgery (see Warnings and Precautions), conjunctivitis, cystoids macular oedema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, blepharoptosis, diplopia and keratitis.

Ear and labyrinth disorders:

Tinnitus.

Cardiac disorders:

Arrhythmia, cardiac arrest, cardiac failure, claudication, cold hands and feet, heart block, palpitation, pulmonary oedema, Raynaud's phenomenon, worsening of angina pectoris, bradycardia, hypotension, oedema, chest pain, congestive heart failure and atrioventricular block.

Vascular disorders: Syncope.

Respiratory, thoracic and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, exacerbation of asthma, dyspnoea, cough, upper respiratory infection and nasal congestion.

Gastrointestinal disorders:

Anorexia, abdominal pain, nausea, dysgeusia, vomiting, diarrhoea and dyspepsia.

Skin and subcutaneous tissue disorders:

Alopecia, exacerbation of psoriasis, psoriasiform rash and skin rash.

Renal and urinary disorders:

Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

Musculoskeletal and connective tissue disorders: Myalgia

Other:

Decreased libido, sexual dysfunction

Post-Marketing Experience

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

Eye disorders:

Vision blurred, visual acuity reduced.

Skin and subcutaneous tissue disorders:

Erythema facial.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Rare reports of overdosage with COMBIGAN® in humans resulted in no adverse outcomes.

Brimonidine tartrate

Ophthalmic overdose:

In those cases, received, the events reported have been generally those already listed as adverse reactions. Symptoms of brimonidine tartrate overdose such as hypotension, bradycardia, hypothermia, coma, hypotonia, lethargy, pallor, respiratory depression, somnolence and apnea have been reported in neonates, infants and children receiving brimonidine tartrate ophthalmic solution as part of medical treatment of congenital glaucoma or by accidental ingestion. Please see Paediatric Use.

Systemic overdose resulting from accidental ingestion:

There is very limited information regarding accidental ingestion of brimonidine in adults. Accidental human adult ingestion of brimonidine tartrate 0.2% has resulted in a hypotensive episode followed by rebound hypertension.

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

Timolol

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

If overdose occurs treatment should be symptomatic and supportive; a patient airway should be maintained. Contact the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on overdose management.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics; other antiglaucoma preparations.

COMBIGAN® is a combination eye drop containing brimonidine tartrate and timolol. Brimonidine tartrate is an alpha-2 selective adrenergic receptor agonist for ophthalmic use and is a white to off-white, pale yellow powder that is water soluble. In solution, brimonidine tartrate has a clear, greenish-yellow colour. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. It is a white to off-white crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

Mechanism of action

COMBIGAN® consists of two active substances: brimonidine tartrate and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. COMBIGAN® has a rapid onset of action with peak effect at 2 hours post dosing.

Pharmacodynamic effects

Brimonidine tartrate

Brimonidine tartrate is an alpha-2 adrenergic agonist that is approximately 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenergic receptor. Affinity at human alpha-1 and alpha-2 adrenoreceptors are ~2000 nM and ~2 nM, respectively. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine solution decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine eye drops have the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine has a rapid onset of action, with the peak ocular hypotensive effect occurring at two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine solution has a dual mechanism of action. Brimonidine lowers IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

Timolol

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant or local anaesthetic (membrane stabilising) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biological response that would occur with stimulation of that receptor. The specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biological response.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Clinical efficacy and safety

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

The efficacy of COMBIGAN® was demonstrated in 4 multicentre, randomised, double-masked parallel group studies.

Study 1 compared twice daily COMBIGAN® eye drops to twice daily TIMOPTOL® (timolol 0.5%) or twice daily ALPHAGAN® (brimonidine tartrate 0.2%). A total of 589 patients were enrolled.

Study 2 compared twice daily COMBIGAN® eye drops to twice daily TIMOPTOL® (timolol 0.5%) and twice daily ALPHAGAN® (brimonidine tartrate 0.2%) administered adjunctively. A total of 371 patients were enrolled.

Table 1: Mean IOP (mmHg) at Baseline and Mean Change from Baseline at each Scheduled Visit (ITT and LOCF) for Study 1 and Study 2

		Study 1			Study 2	
Timepoint		**COMBIGAN® (BID) (N=196)**	**Brimonidine tartrate (BID) (N = 202)**	**Timolol (BID) (N = 191)**	**COMBIGAN® (BID) (N = 188)**	**Adjunctive (BID) (N = 183)**
Baseline	Hour 0	24.8	24.5 (-0.10, 0.81)	24.8 (-0.49, 0.44)	25.0	25.0 (-0.41, 0.68)
	Hour 2	22.2	21.7 (-0.13, 1.03)	21.7 (-0.12, 1.05)	22.6	22.4 (-0.31, 0.81)
Week 12	Hour 0	-4.3	-2.7 [a] (-2.18, -0.79)	-3.9 (-1.06, 0.34)	-4.9	-4.9 (-0.60, 0.79)
	Hour 2	-5.0	-4.0 [a] (-1.64, -0.13)	-3.0 [b] (-2.73, -1.19)	-5.3	-5.3 (-0.66, 0.61)

[a] $p < 0.05$ for COMBIGAN® vs brimonidine tartrate

[b] $p < 0.05$ for COMBIGAN® vs timolol

(95% CI)

In Study 1, there were no statistically significant differences in the mean values of Hour 0 and Hour 2 at baseline between the 3 groups. The mean decreases from baseline IOP were statistically significant within each treatment group at each follow-up timepoint ($p < 0.001$). The mean decrease from baseline IOP was statistically significantly greater with COMBIGAN® than with brimonidine tartrate at Hour 0 and 2 at all follow-up visits ($p \leq 0.022$). At the primary timepoint of Hour 0, Week 12, a difference of 1.49 mmHg from baseline IOP favouring COMBIGAN® over brimonidine tartrate was seen. This can be considered to be a clinically significant difference. There was no statistically significant difference in the mean decrease from baseline IOP between COMBIGAN® and timolol at Hour 0 at any follow-up visit ($p \geq 0.055$), however the mean decreases from baseline IOP for COMBIGAN® were always numerically superior at Hour 0 at all visits.

The mean decrease from baseline IOP was statistically significantly greater with COMBIGAN® than with timolol at hour 2 at all follow-up visits ($p < 0.001$). Clinically significant differences of at least 1.5 mmHg in mean change from baseline IOP favouring COMBIGAN® over timolol were seen at hour 2 at all follow-up visits.

In Study 2, the mean values of Hour 0 and Hour 2 at baseline were similar between the 2 groups, with no significant differences. Mean changes from baseline IOP at Weeks 2, 6 and 12 ranged from -4.4 to -5.3 mmHg in both treatment groups. At Week 12 the mean change from baseline in Hour 0 IOP (primary efficacy endpoint) was -4.9 mmHg for both groups. The upper limit of the 95% CI for the difference in the COMBIGAN® minus the adjunctive groups was below 1.5 mmHg, the criterion for non-inferiority, demonstrating that the COMBIGAN® group was non-inferior to the adjunctive group. The mean decreases from baseline IOP at both Hour 0 and Hour 2 were also statistically significant at all follow-up visits within each treatment group ($p<0.001$). Thus, noninferiority of the COMBIGAN® group compared with the adjunctive group was demonstrated at all timepoints.

Studies 3 and 4 compared twice daily COMBIGAN® with that of twice daily TIMOPTOL® (timolol 0.5%) or ALPHAGAN® (brimonidine tartrate 0.2%) three times daily administered for 12 months in patients with glaucoma or ocular hypertension. A total of 1159 patients were enrolled.

Table 2: Mean IOP (mmHg) at Baseline and Mean Change from Baseline at each Scheduled Visit (ITT and LOCF) for Study 3 and Study 4

		Study 3			Study 4		
Timepoint		**COMBIGAN® (BID) (N = 192)**	**Brimonidine tartrate (TID) (N = 186)**	**Timolol (BID) (N = 195)**	**COMBIGAN® (BID) (N = 193)**	**Brimonidine tartrate (TID) (N = 196)**	**Timolol (BID (N = 197)**
Baseline	Hour 0	24.5	24.7 (-0.73, 0.31)	25.1[a] (-1.08, -0.05)	24.9	25.0 (-0.64, 0.42)	24.8 (-0.42, 0.63)
	Hour 2	22.8	23.2 (-1.03, 0.19)	23.5[a] (-1.22, -0.01)	23.7	23.7 (-0.56, 0.62)	23.6 (-0.44, 0.74)
	Hour 7	21.6	22.0 (-1.04, 0.29)	22.6[a] (-1.56, -0.24)	22.6	23.0 (-1.07, 0.14)	22.4 (-0.47, 0.75)
	Hour 9	21.4	21.9 (-1.17, 0.15)	22.5[a] (-1.68, -0.37)	22.2	22.5 (-0.98, 0.25)	22.3 (-0.77, 0.45)
Month 12	Hour 0	-6.0	-3.4[b] (-3.32, -1.91)	-5.2[c] (-1.72, -0.37)	-6.1	-3.2[a] (-3.59, -2.17)	-5.5 (-1.31, 0.10)
	Hour 2	-6.9	-5.0[b] (-2.57, -1.19)	-4.8[c] (-3.00, -1.73)	-7.5	-5.0[a] (-3.12, -1.73)	-5.3[b] (-2.88, -1.49)
	Hour 7	-4.7	-2.2[b] (-3.21, -1.75)	-3.8[c] (-2.07, -0.81)	-5.1	-3.2[a] (-2.54, -1.30)	-4.1[b] (-1.67, -0.43)
	Hour 9	-4.1	-4.4 (-0.36, 0.98)	-3.6[c] (-1.62, -0.44)	-4.7	-4.1 (-1.23, 0.07)	-4.1 (-1.22, 0.08)

[a] = Combination mean IOP at baseline statistically significantly lower than timolol ($p \leq 0.046$)

[b] = Combination mean decrease in IOP from baseline statistically significantly greater than brimonidine tartrate ($p < 0.001$)

[c] = Combination mean decrease in IOP from baseline statistically significantly greater than timolol ($p \leq 0.026$). (95% CI)

In Study 3, the mean decrease from baseline diurnal IOP was statistically significantly greater with COMBIGAN® than with brimonidine tartrate at Hours 0, 2, and 7 at all follow-up visits ($p < 0.001$). In addition, clinically significant differences of more than 1.5 mmHg in mean change from baseline IOP favouring COMBIGAN® over brimonidine tartrate were seen at Hours 0, 2 and 7 at all follow-up visits. There was no statistically significant difference in the mean decrease from baseline IOP between COMBIGAN® and brimonidine tartrate at Hour 9 at any follow-up visit ($p \geq 0.339$).

The mean decrease from baseline diurnal IOP was statistically significantly greater with COMBIGAN® than with timolol at Hours 0, 2, 7 and 9 at all follow-up visits ($p \leq 0.026$). In addition, clinically significant differences of more than 1.5 mmHg in mean change from baseline IOP favouring COMBIGAN® over timolol were seen at Hours 0, 2, 7 and 9 (Week 2, Months 6 and 12), at Hours 0, 2 and 7 (Month 3), at Hours 2 and 7 (Week 6) and at Hour 2 (Month 9).

In Study 4, the mean decrease from baseline diurnal IOP was statistically significantly greater with COMBIGAN® than with brimonidine tartrate at Hours 0, 2 and 7 at all follow-up visits (except Month 9, Hour 7, when IOP was not measured) ($p<0.001$). In addition, clinically significant differences of more than 1.5 mmHg in mean change from baseline IOP favouring COMBIGAN® over brimonidine tartrate were seen at Hours 0, 2 and 7 at all follow-up visits. There was no statistically significant difference in the mean decrease from baseline IOP between COMBIGAN® and brimonidine tartrate at Hour 9 at any follow-up visit ($p \geq 0.082$).

The mean decrease from baseline diurnal IOP was statistically significantly greater with COMBIGAN® than with timolol at hours 0, 2 and 7 at all follow-up visits (except Hour 0 at Month 12) and at Hour 9 at Week 2, Week 6 and month 3 ($p \leq 0.046$). In addition, clinically significant differences of more than 1.5 mmHg in mean change from baseline favouring COMBIGAN® over timolol were seen at Hours 0, 2 and 7 (Week 2); at Hours 2 and 7 (Week 6, Months 6 and 12) and at Hour 2 (Months 3 and 9).

Over 12 weeks of study treatments, approximately 10% of patients on combination treatment reached and maintained an IOP of ≤18 mmHg, compared to 5.4% with brimonidine alone ($p=0.077$ vs combination) and 9.4% with timolol alone ($p=0.779$). Similarly, the number of patients achieving target IOP of ≤18 mmHg was similar in the combination and adjunctive treatment groups (6.9% and 9.3% with combination and adjunctive treatments, respectively, $p=0.402$). However, over 12 months of treatment, the number of patients achieving and maintaining target IOP (≤18 mmHg) was significantly greater in the combination group (10%13%) compared to the brimonidine group (1.5%) in both Study 3 and Study 4. Combination treatment was significantly superior to timolol (13.5% vs 5.6%) in Study 3 only.

Pharmacokinetic properties

Combigan

Plasma brimonidine and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to COMBIGAN® treatment in healthy subjects. There were no statistically significant differences in brimonidine or timolol AUC between COMBIGAN® and the respective monotherapy treatments. Mean plasma C_{max} values for brimonidine and timolol following dosing with COMBIGAN® were 0.0327 and 0.406 ng/mL respectively.

Studies in healthy subjects and patients revealed that compared to monotherapy with brimonidine and timolol, there was a tendency for reduced systemic exposure to both brimonidine and timolol following treatment with COMBIGAN®. The absorption of timolol was delayed following combination treatment compared to monotherapy (2.4 vs 1.4 hours). Following treatment with combination eye drops, the systemic concentrations of brimonidine and timolol were significantly higher in females and elderly patients.

Brimonidine tartrate

After ocular administration of a 0.2% solution twice daily in normal healthy subjects for 10 days, plasma concentrations were measured as (mean) C_{max} 0.06 ng/mL. Plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

Brimonidine is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of the radioactivity following an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Timolol

After ocular administration of a 0.25% eye drop to humans, peak timolol concentration in the aqueous humor was 1.56 µg/mL at 1-hour post dose. The half-life of timolol in plasma is about 7 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

6. PHARMACEEUTICAL PARTICULARS

6.1 List of excipients

PRESERVATIVE: benzalkonium chloride

INACTIVES: dibasic sodium phosphate heptahydrate, monobasic sodium phosphate monohydrate, hydrochloric acid or sodium hydroxide, purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life:

15 months

6.4 Special precautions for storage:

Store below 25°C. Protect from light.

Discard contents 4 weeks after opening the bottle.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

6.5 Nature and contents of container

COMBIGAN® eye drops are supplied in white opaque plastic dropper bottles (5mL). Each mL of COMBIGAN® contains 2 mg of brimonidine tartrate and 5 mg of timolol (6.83 mg of timolol maleate)

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand
Toll free telephone: 0800 659 912

9. DATE OF FIRST APPROVAL

October 2005

10. DATE OF REVISION OF THE TEXT

08 May 2023

SUMMARY TABLE OF CHANGES

Sections Changed	Summary of new information
8	Change in Sponsor