VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology (Glaucoma) Glaucoma is an eye disease usually associated with an increased fluid pressure inside the eyes that can damage the sensory eye nerve, leading to vision loss or even blindness if untreated. Of the two types of glaucoma, open-angle is the most common form (90% of glaucoma) and usually develops slowly as the eye's drainage canals gradually become clogged. Acute (or closed) angle glaucoma occurs when the drainage canal get blocked or covered due to the closed angle between the colored part of eye (iris) and eye surface (cornea).

Glaucoma can rarely affect children. It usually develops after 40 years of age, and becomes more common with advancing age. Glaucoma affects one in 200 people aged 50 and younger, and one in 10 over the age of eighty. Currently, glaucoma accounts for 12% of all global blindness (Resnikoff, S. et al. 2004).

VI.2.2 Summary of Treatment Benefits

Current (gold) standard of treatment: Most common first line treatment for glaucoma is topical eye drops that must be taken regularly. The currently available eye drops to treat glaucoma, include beta-blockers, dorzolamide, brimonidine, pilocarpine, prostaglandin analogs, and epinephrine, which can be prescribed alone or together in combination of several eye drops (Vass, C. et al. 2007). The most common type of surgical treatment for glaucoma is drainage surgery involving making a trapdoor that allows fluid to drain from the eye. Complications associated with surgery can occur which may fail in long-term treatment of glaucoma due to scarring (Burr, J. et al. 2012).

When treatment with COMBIGAN is considered: COMBIGAN is indicated for the reduction of pressure in the eyes (IOP) for patients with open-angle glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP with other medication therapy such as topical beta-blockers.

Most important ('pivotal') studies conducted with COMBIGAN: COMBIGAN has been studied in 6 main clinical trials involving 809 patients with glaucoma or increase pressure in the eye, who received COMBIGAN for at least 7 days and up to 12 months. In these 6 clinical trials, COMBIGAN consistently decreases pressure in the eye throughout the day and throughout the study. COMBIGAN has consistently demonstrated to be more effective than the treatment with either brimonidine or timolol alone.

VI.2.3 Unknowns Relating to Treatment Benefits

In order to minimize ambiguity in the interpretation of the results and to protect patient safety, limitations are inherent in the scope of clinical trials, primarily due to the exclusion of certain populations; however, there is no evidence to suggest efficacy differences in the target population.

VI.2.4 Summary of Safety Concerns

Table 10–1 Important Identified Risks

Important Identified Risk	What is known	Preventability
Allergic reactions to active or inactive ingredients, including serious allergic reaction which causes difficulty in breathing or dizziness and localized allergic reaction in the eye	Hypersensitivity reactions can vary from mild symptoms to serious and/or immediate severe reactions that could be life-threatening, such as anaphylaxis. Serious allergic reactions have been rarely reported with COMBIGAN. Symptoms usually occur with a short time after instillation, and can range from mild local reactions such as irritation/burning to more serious reactions such as swelling of the face or throat, or severe skin problems.	Yes, The doctor's prescribing information for COMBIGAN® states that it should not be used in patients allergic (hypersensitive) to active ingredient (brimonidine and timolol) or inactive ingredient (benzalkonium chloride) of COMBIGAN
Respiratory reactions (including: difficulty breathing, shortness of breath, wheezing, severe lung disease which may cause wheeziness, difficulty in breathing and/or long‑standing cough) in patients with existing asthma or long standing cough	Like other topically applied eye drops, the active substances (timolol/brimonidine) in COMBIGAN may be absorbed into the blood stream. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some eye drops containing beta-blockers.	Yes, The doctor's prescribing information for COMBIGAN® states that it should not be used in patients who have bronchospasm, bronchial asthma or have a history of bronchial asthma or other lung disease.
Heart rhythm disturbances and heart failure (symptoms vary from severity including slow heart rate, fainting, shortness of breath, low blood pressure).	Eye drop containing beta-blockers like COMBIGAN may be absorbed into the blood stream and can cause worsening of the condition in patients with unstable heart diseases (including disturbances in heart rhythm and heart failure).	Yes, before using COMBIGAN, tell your doctor if you have heart problems such as low heart rate, heart failure, heart beat disorders (unless controlled by a pacemaker).
Decrease in mental alertness including sleepiness, floppiness, low body temperature, paleness and breathing difficulties (Central nervous system depression) in children,	Brimonidine and Timolol have been linked with systemic side effect representing Central Nervous system depression. Children are at greater risk for systemic side effects because ocular dosing is not weight-adjusted, and infants are especially vulnerable as a consequence of the inability to	Yes, COMBIGAN is not approved to be used in infants and neonates. Children of 2 years of age and above, especially those in the 2-7 age range and/or

Important Identified Risk	What is known	Preventability
particularly in neonates and infants (Off-label use)	efficiently metabolize the drug, and/or an immature blood-brain barrier.	weighing ≤20 Kg, should be treated with caution and closely monitored.

Table 10–2 Important Potential Risks

Important potential Risks	What is known (Including reason why it is considered a potential risk)
Heart diseases (symptoms varies from severity, including chest pain and low blood pressure)	Eye drops containing Beta-blocker may be absorbed into the blood stream and can cause worsening of the condition in patients with unstable heart diseases (including chest pain, heart failure and low blood pressure. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.
Potential reactions with other medications used to treat high blood pressure, irregular heartbeat, heart diseases, depression and anesthesia for surgery.	The effects of eye drops containing beta-blocker (including COMBIGAN) may increase resulting in low blood pressure and/or slow heart rate when used together with following types of medications: MAOIs, TCA, SNRIs, mianserin) or CYP2D6 inhibitors (e.g. SSRIs), anti-arrhythmics (e.g. cardiac glycosides, verapamil, diltiazem, systemic beta-blockers), and surgical anaesthesia (COMBIGAN SmPC, Section 4.4).
Poor circulation in extremities (cold hand &feet) in patients with pre-existing condition.	Patients with severe peripheral circulatory disturbance /disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution (COMBIGAN SmPC, Section 4.4)
Dry eyes in patients with eye diseases.	There is insufficient evidence to support causal relationship between COMBIGAN and dry eyes in patients, however, preservatives used in eye drops may reduce tear film break up time. Severity of dry eye may vary from discomfort and intermittent blurred vision to severe sight threatening front of the eye (corneal) ulcer in rare cases.
Masking symptoms of thyroid hyperactivity or adrenal gland tumor (phaeochromocytoma) in patients with pre-existing condition.	Eye drops containing beta-blockers may mask the signs of hyperthyroidism. COMBIGAN must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma (COMBIGAN SmPC, Section 4.4).
Masking low blood sugar (hypoglycemia) symptoms in patients with uncontrolled diabetes.	Beta-blockers eye drops should be administered with caution in patients subject to spontaneous hypoglycaemia (labile diabetes), as beta-blockers may mask the signs and symptoms of acute hypoglycaemia (COMBIGAN SmPC, Section 4.4).

Important potential Risks	What is known (Including reason why it is considered a potential risk)
A build-up of fluid between the blood vessel layer and the white surface of the eye (choroidal detachment) producing a blister-like bulge, which can lead to visual loss.	Choroidal detachment is associated with eye surgery, in which the pressure within the eye is extremely low and has been reported with aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration eye procedures, but was not reported in clinical trials for COMBIGAN.

Table 10–3 Important Missing Information

Important Missing Information	What is known
Limited information on use during Pregnancy and Lactation	• As no adequate and well-controlled studies with COMBIGAN in pregnant women, COMBIGAN should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. • As timolol eye drops is detected in human milk and brimonidine is excreted in the milk of the lactating rat, a decision therefore should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Limited information on use in patients with 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. • In patients with severe renal impairment on dialysis, treatment with timolol (a beta-blocker component of COMBIGAN) has been associated with pronounced hypotension (low blood pressure).

VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

There are no additional risk minimisation measures by safety concerns beyond routine pharmacovigilance activities COMBIGAN.

VI.2.6 Planned Post-Authorisation Development Plan

There are no on-going or planned additional pharmacovigilance studies/activities for COMBIGAN in terms of efficacy studies and further investigation of safety concerns as of the data-lock-point of this RMP (31 March 2013). As aforementioned, there are no imposed, mandatory additional pharmacovigilance activities or studies required to fulfill specific safety concerns or efficacy related obligation for marketing approval of COMBIGAN.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 10–4 Major Changes to the Risk Management Plan Over Time

Version	Date	Safety concerns	Comments
1.0	Oct 2013	**Important Identified risks** • Cardiovascular events: Bradycardia, Hypotension • Somnolence **Important Potential risks**: • Iridocyclitis, Iritis, Uveitis • Asthma, Bronchospasm • Cardiac events: Cardiac failure, Angina, Cardiac conduction disorders • Choroidal detachment/Choroidal effusion • Drug interaction with systemic calcium-channel blockers, beta-blockers, anti-hypertensives, anti-arrhythmics, digitalis glycosides, guanethidine, CYP2D6 inhibitors and tricyclic antidepressants. **Important Missing Information:** • Use during Pregnancy and Lactation • Paediatric Use • Use in Patients with renal and hepatic impairment • Use in Patients with cardiac conduction disorders • Use in patients on antidepressants	Initial RMP submission
2.0	Oct 2014	**Important Identified Risks** 1- Additional safety concerns added to important identified risk category: • Hypersensitivity Reactions to Active Substances or Excipients: Localized Ocular Hypersensitivity Reactions (e.g., Conjunctivitis, Uveitis, Iritis and Delayed Iridocyclitis) and Systemic Hypersensitivity Reactions (including Allergic Anaphylaxis) • Safety in children off-label use: (CNS depression, particularly in neonates and infants) 2- Safety concern reclassified from important potential risk to important identified risk with revision of wording: • Reactive airway events (e.g. bronchospasm, dyspnoea, wheezing) in patients with pre-existing asthma or chronic obstructive pulmonary disease (COPD). • Cardiac conduction disorders and symptomatic heart failure **Important Potential Risks** 1- Safety concerns added as important potential risks: • Severe peripheral vascular disorders • Uncontrolled hyperthyroidism or phaeochromocytoma. • Poorly controlled diabetes mellitus • Corneal disorders (risk of dry eyes) • Cardiovascular disease: Ischaemic heart disease and hypotension	Address the Rapporteur's recommendations in regards to important identified risks, important potential risks and missing information as agreed for COMBIGAN based on available safety data from clinical studies, over 10-year postmarketing surveillance and literature review.

Version	Date	Safety concerns	Comments
		2- Revision of existing important potential risk “Drug interaction” to include SNRIs and Surgical anaesthesia, as follow: • Drug interactions, including antidepressant therapy that alters noradrenergic transmission (e.g. MAOIs, TCA, SNRIs, mianserin) or CYP2D6 inhibitors (e.g. SSRIs), anti-arrhythmics (e.g. cardiac glycosides, verapamil, diltiazem, systemic beta-blockers and surgical anaesthesia. **Missing Information** • Removed “Paediatric Use, Use in patients with cardiac conduction disorders and Use in patients on antidepressants” from Missing Information category.	