[BIMATOPROST/TIMOLOL] 0.3 MG/ML + 5 MG/ML, PRESERVATIVE FREE EYE DROPS, SOLUTION

RISK MANAGEMENT PLAN

BIMATO/TIMO PF-v1-091116

TABLE OF CONTENTS

Active substance(s) (INN or common name):	**Bimatoprost-timolol**
Pharmaco-therapeutic group (ATC Code):	**S01ED51**
Name of Marketing Authorisation Holder or Applicant:	**Pharmathen SA**
Number of medicinal products to which this RMP refers:	**3**
Product(s) concerned (brand name (s)): **DK/H/2710/001/DC** (DK, DE, IT) **DK/H/2715/001/DC** (DK, CY, EL)	 **Bimatoprost/Timolol Pharmathen** (DK, DE, IT) **Lenigron** (DK, CY, EL)

Active substance(s) (INN or common name):	**Bimatoprost-timolol**
Pharmaco-therapeutic group (ATC Code):	**S01ED51**
Name of Marketing Authorisation Holder or Applicant:	**HORUS PHARMA**
Number of medicinal products to which this RMP refers:	**1**
Product(s) concerned (brand name (s)): **DK/H/2712/001/DC** (DK, FR, BE, NL, LU)	 **Bimatoprost/Timolol Horus Pharma** (DK, FR, BE, NL, LU)

Active substance(s) (INN or common name):	**Bimatoprost-timolol**
Pharmaco-therapeutic group (ATC Code):	**S01ED51**
Name of Marketing Authorisation Holder or Applicant:	**PharmaSwiss Česká republika s.r.o.**

Number of medicinal products to which this RMP refers:	**1**
Product(s) concerned (brand name (s)): **DK/H/2711/001/DC** (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, CZ, SI, LV)	 **Vizibim Duo** (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, CZ, SI, LV)

Data lock point for this RMP 20.09.2016 Version number BIMATO/TIMO PF-v1-091116

Date of final sign off 23.09.2016

RISK MANAGEMENT PLAN

PART I: PRODUCT(S) OVERVIEW

[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative free eye drops, solution

Administrative information on the RMP

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted/or Not Applicable**
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	-	Not applicable
	SII Non-clinical part of the safety specification	-	Not applicable
	SIII Clinical trial exposure	-	Not applicable
	SIV Populations not studied in clinical trials	-	Not applicable
	SV Post-authorisation experience	-	Not applicable
	SVI Additional EU requirements for the safety specification	-	Not applicable
	SVII Identified and potential risks	-	Not applicable
	SVIII Summary of the safety concerns	-	Not applicable
Part III Pharmacovigilance Plan	Only needed if reference product has additional PhV activities	-	Not applicable
Part IV Plan for post-authorisation efficacy studies	Only needed if reference product has imposed post-authorisation efficacy studies	-	Not applicable
Part V Risk minimization Measures		-	Not applicable
Part VI		-	Not applicable

Summary of RMP			
Part VII Annexes	ANNEX 1 Eudravigilance Interface	-	Not applicable
	ANNEX 2 Current or proposed SmPC/PIL	09/2016	Not applicable
	ANNEX 3 Worldwide marketing status by country	-	Not applicable
	ANNEX 4 Synopsis of on-going and completed clinical trial programme	-	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study program	-	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	-	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	-	Not applicable
	ANNEX 8 Protocols for studies in Part IV	-	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	-	Not applicable
	ANNEX 10 Details of proposed additional risk minimization activities	-	Not applicable
	ANNEX 11 Mock up examples	-	Not applicable
	ANNEX 12 Other supporting data	Please refer to page 121 of this document	Not applicable

QPPV name	
QPPV signature	
Contact person for this RMP	
E-mail address or telephone number of contact person	

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Contact person for this RMP	
E-mail address or telephone number of contact person	

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QPPV signature	
Contact person for this RMP	
E-mail address or telephone number of contac t person	

Overview of versions:

Version number of last agreed RMP:	-
Version number	BIMATO/TIMO PF-v1-091116
Agreed with	DK/H/2710/001/DC DK/H/2715/001/DC DK/H/2711/001/DC DK/H/2712/001/DC

Current RMP versions under evaluation:

Not applicable.

Invented name (s) in the European Economic Area (EEA)	Bimatoprost/Timolol Pharmathen 0.3 mg/ml + 5 mg/ml, eye drops, solution (DK, DE, IT) Lenigron 0.3 mg/ml + 5 mg/ml, eye drops, solution (DK, CY, EL) Bimatoprost/Timolol Horus Pharma 0.3 mg/ml + 5 mg/ml, eye drops, solution (DK, FR, BE, NL, LU) Vizibim Duo 0.3 mg/ml + 5 mg/ml, eye drops, solution (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, CZ, SI, LV)
Authorisation procedure	DK/H/2710/001/DC DK/H/2715/001/DC DK/H/2712/001/DC DK/H/2711/001/DC
Brief description of the product including:	
• Chemical class	Pharmacotherapeutic group: Ophthalmologicals, Beta blocking agents, timolol combinations. – ATC code: S01ED51
• Summary of mode of action	[Invented name] consists of two active substances: bimatoprost and timolol. 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. Bimatoprost/timolol has a rapid onset of action. Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin F2α (PGF2α) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Timolol is a beta1 and beta2 non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased

• Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Not applicable.
Indication (s) in the EEA Current (if applicable)	Not applicable.
Proposed (if applicable)	Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
Posology and route of administration in the EEA Current (if applicable)	Not applicable.
Proposed (if applicable)	*Recommended dosage in adults (including older people)* The recommended dose is one drop of [Invented name] in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day. Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing. If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. *Renal and hepatic impairment* Bimatoprost/timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients. *Paediatric population* The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.

	Method of administration If more than one topical ophthalmic medicinal product is to be used, each one should be instilled at least 5 minutes apart. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity. [Invented name] eye drops solution is a sterile solution that does not contain a preservative. Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye. Patients should also be instructed that ocular solutions, if handled improperly, 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 solutions.
Pharmaceutical form (s) and strengths Current (if applicable)	Not applicable.
Proposed (if applicable)	*[Invented name] 0.3 mg/mL + 5 mg/mL eye drops, solution* Eye drops, solution. Clear, colorless aqueous solution. One mL of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

Country and date of first authorization worldwide	-	-
Country and date of first launch worldwide	-	-
Country and date of first authorization in the EEA	-	-

Is the product subject to additional monitoring in the EU? Yes [ ] No [√]

PART II: SAFETY SPECIFICATION

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative free eye drops, solution' is a generic formulation of *Ganfort® (Allergan)*. This is being a 'hybrid' application under the Article 10(3) of European Directive 2001/83/EC. Therefore, all Modules of Part II (from module SI to Module SVIII) are applicable.

MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S):

Indication: *"[Bimatoprost/Timolol] 0.3mg/mL + 5mg/mL, eye drops, solution"* is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Brand names of concerned products (with this indication):

- Bimatoprost/Timolol Pharmathen 0.3 mg/ml + 5 mg/ml, eye drops, solution
- Lenigron 0.3 mg/ml + 5 mg/ml, eye drops, solution
- Bimatoprost/Timolol Horus Pharma 0.3 mg/ml + 5 mg/ml, eye drops, solution
- Vizibim Duo 0.3 mg/ml + 5 mg/ml, eye drops, solution

SI.1 EPIDEMIOLOGY OF THE DISEASE

Epidemiology of the indication (s) and target population (s)

Indication/target population	**Ocular hypertension** (OHT) is a condition of intraocular pressure that is higher than normal but that has not resulted in a constricted visual field or increased cupping of the optic nerve head.
Incidence of target population	Studies estimate that 3-6 million people in the United States alone, including 4-10% of the population older than 40 years, have intraocular pressures of 21 mm Hg or higher, without detectable signs of glaucomatous damage using current tests. Ocular hypertension is 10-15 times more likely to occur than primary open-angle glaucoma, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will have pressures higher than 21 mm Hg, but only 1 of those people will have glaucoma. Over a 5-year period, several studies have shown the incidence of glaucomatous damage in people with ocular hypertension to be about 2.6-3% for intraocular pressures of 21-25 mm Hg, 12-26% for intraocular pressures of 26-30 mm Hg, and approximately 42% for those higher than 30 mm Hg.

	In approximately 3% of people with ocular hypertension, the veins in the retina can become blocked (called a retinal vein occlusion), which could lead to vision loss. Some studies have found that the average intraocular pressure in blacks is higher than in whites, while other studies have found no difference. • A 4-year study showed that blacks with ocular hypertension were 5 times more likely to develop glaucoma than whites. Findings suggest that, on average, blacks have thinner corneas, which may account for this increased likelihood to develop glaucoma, as a thinner cornea may cause pressure measurements in the office to be falsely low. • In addition, blacks are considered to have a 3-4 times greater risk of developing primary open-angle glaucoma. They are also believed to be more likely to have optic nerve damage. Although some studies have reported a significantly higher average intraocular pressure in women than in men, other studies have not shown any difference between men and women. • Some studies suggest that women could be at a higher risk for ocular hypertension, especially after menopause. • Studies also show that men with ocular hypertension may be at a higher risk for glaucomatous damage.
Prevalence of target population	Population studies such as the Framingham, Beaver Dam, Baltimore, Rotterdam, Barbados, and Egna-Neumarkt studies have estimated that 4-10% of the population older than 40 years will have intraocular pressure (IOPs) of 21 mm Hg or higher without detectable signs of glaucomatous damage. Ocular hypertension has a 10-15 times greater prevalence than pseudoexfoliative glaucoma (POAG)
Mortality in target indication	Ocular hypertension systemic morbidity and mortality can result from the possible cardiopulmonary adverse effects of intraocular pressure (IOP)-lowering medications. With regard to ocular morbidity and mortality, retinal vascular occlusion may occur in approximately 3% of ocular hypertensive patients.
Potential health risk	The Ocular Hypertension Treatment Study (OHTS) states that over a 5-year-period, patients with ocular hypertension and intraocular pressure (IOP) levels of 24 mm Hg or more have a 10% overall risk of developing glaucoma. This risk can be cut in half by medical treatment. In 2004, more than 2 million individuals in the United States were diagnosed as having open-angle

	glaucoma. This number is projected to increase to more than 3 million by 2020
Demographic profile of target population	**1. Race-related demographics** Although black individuals are considered to have a 3-4 times higher prevalence of primary open-angle glaucoma (POAG) and larger cup-to-disc ratios compared with white individuals, the data are less clear concerning ocular hypertension. The Barbados Eye Study found the incidence of intraocular pressure (IOPs) greater than 22 mm Hg to be 5 times higher in blacks than in whites. The Baltimore Eye Survey found no difference in mean intraocular pressure between blacks and whites. The Los Angeles Latino Eye Study found Latinos to be at higher risk of ocular hypertension than non-Latino whites but lower than blacks. **2. Sex-related demographics** The Barbados Eye Study found ocular hypertension present more frequently in women. **3. Age-related demographics** Mean intraocular pressure slowly rises with increasing age. Age older than 40 years is considered a risk factor for the development of ocular hypertension and primary open-angle glaucoma.
References	Anne Chang-Godinich, Ocular hypertension medications. http://emedicine.medscape.com Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol*. Aug 1997;115(8):1051-7. Chihara E. Assessment of true intraocular pressure: the gap between theory and practical data. *Surv Ophthalmol*. May-Jun 2008;53(3):203-18. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. Aug 1991;109(8):1090-5. Varma R, Wang D, Wu C, et al. Four-year incidence of open-angle glaucoma and ocular hypertension: the los angeles latino eye study. *Am J Ophthalmol*. Aug 2012;154(2):315-325.e1.

Indication/target population	**Primary open angle glaucoma (POAG)** Primary open-angle glaucoma is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an anterior chamber angle that is open by gonioscopic appearance.
Incidence of target population	Estimates vary as to the conversion rate from OHT to POAG, depending on subject selection and diagnostic criteria. It is likely that approximately 10% of individuals with persistent OHT will convert to POAG over a ten-year period. Risk factors for the conversion of OHT to POAG can be divided into ocular and systemic. Over a 5-year period, several studies have shown the incidence of glaucomatous damage in people with ocular hypertension to be about 2.6-3% for intraocular pressures of 21-25 mm Hg, 12-26% for intraocular pressures of 26-30 mm Hg, and approximately 42% for those higher than 30 mm Hg. In approximately 3% of people with ocular hypertension, the veins in the retina can become blocked (called a retinal vein occlusion), which could lead to vision loss.
Prevalence of target population	Studies estimate that 3-6 million people in the United States alone, including 4-10% of the population older than 40 years, have intraocular pressures of 21 mm Hg or higher, without detectable signs of glaucomatous damage using current tests. Studies over the last 20 years have helped to characterize those with ocular hypertension. Recent data on people with ocular hypertension from the Ocular Hypertension Treatment Study have shown that they have an average estimated risk of 10% of developing glaucoma over 5 years. This risk may be decreased to 5% (a 50% decrease in risk) if eye pressure is lowered by medications or laser surgery. However, the risk may become even less than 1% per year because of significantly improved techniques for detecting glaucomatous damage. Patients with thin corneas may be at a higher risk for glaucoma development. Ocular hypertension is 10-15 times more likely to occur than primary open-angle glaucoma, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will have pressures higher than 21 mm Hg, but only 1 of those people will have glaucoma.

Mortality in target indication	Population-based cohort study of 4092 black participants (aged 40-84 years at baseline) in the Barbados Eye Studies. Open-angle glaucoma was defined by visual field defects and optic disc damage, based on standardized examinations and photograph gradings. Ocular hypertension was defined by an intraocular pressure greater than 21 mm Hg or treatment, without OAG damage. Mortality was ascertained from death certificates. Cox proportional hazards regression analyses determined associations with mortality. In this black population, cardiovascular mortality tended to increase in persons with previously diagnosed/treated OAG and ocular hypertension. The excess mortality associated with timolol maleate treatment of OAG, also found in a white population, warrants further investigation
Potential health risk	Ocular hypertension cannot be prevented, but through regular eye examinations with an ophthalmologist, its progression to glaucoma can be prevented. Glaucoma is the second largest cause of blindness worldwide, estimated to affect 60.5 million people. It is also the leading cause of irreversible visual loss. By 2020, the number of glaucoma sufferers is estimated to increase to approximately 80 million. In the USA, for example, a 50% increase in the prevalence of glaucoma is expected by 2020. Risk factors for open-angle glaucoma include increased age, African ethnicity, family history, increased intraocular pressure, myopia, and decreased corneal thickness.
Demographic profile of target population	A 40-Year Forecast of the Demographic Shift in Primary Open-Angle Glaucoma in the United States estimates that there will be a substantial increase in the number of persons with POAG in the United States, from 2.71 million in 2011 to 7.32 million in 2050. ***By age* group**, the highest proportion will continue to be contributed by those aged 70–79 years (31% in 2011 vs. 32% in 2050). **By sex**, the estimated number of women to men affected by POAG will decrease from 2011 (women: 1.43 million; men: 1.28 million) to 2050 (women: 3.68 million; men: 3.64 million). ***By race and ethnicity***, the highest proportion of the number of persons with POAG will shift from non-

	Hispanic whites (44%) in 2011 to Hispanics (50%) in 2050. The single largest demographic group shift will be from non-Hispanic white women in 2011 (24.7%) to Hispanic men in 2050 (25.4%).
References	Annette Giangiacomo, Anne Louise Coleman, The Epidemiology of Glaucoma Chapter 2 Murray F, American Optometric Association-OAG Jerald A Bell, MD, Ocular Hypertension http://www.emedicinehealth.com/ocular_hypertension Wu SY, Nemesure B, Hennis A, Schachat AP, Hyman L, Leske MC; Barbados Eye Studies Group.Open-angle glaucoma and mortality: The Barbados Eye Studies. Arch Ophthalmol. 2008 Mar; 126(3):365-70. Doi: 10.1001/archophthalmol.2007.77 Mukhtar Bizrah, Li Guo, Maria Francesca Cordeiro. Glaucoma and Alzheimer's Disease in the Elderly. Aging Health. 2011;7(5):719-733 Anne Chang-Godinich, Ocular hypertension medications. http://emedicine.medscape.com Thasarat S. Vajaranant, Shuang Wu, Mina Torres, and Rohit Varma. A 40-Year Forecast of the Demographic Shift in Primary Open-Angle Glaucoma in the United States. IOVS, Special Issue 2012, Vol. 53, No. 5

SI.2 CONCOMITANT MEDICATION(S) IN THE TARGET POPULATION

As indicated in section SI.3 below, comorbidities are Alzheimer's disease (AD), hypertension, heart failure, hyperlipidemia, diabetes, airways disease and depression. Concomitant medications are therefore quite wide-ranging but likely to include antihypertensives (thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers), antihyperlipidemic drugs (i.e. statins, fibrates, bile acid sequestrants), antidiabetics (insulin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones and biguanides) and NSAIDs. Five medications are currently used to treat the cognitive problems of AD: four are acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil) and the other (memantine) is an NMDA receptor antagonist.

SI.3 IMPORTANT CO-MORBIDITIES FOUND IN THE TARGET POPULATION

Comorbidity of Glaucoma and Alzheimer's disease
Primary open angle glaucoma (POAG) and Alzheimer's disease (AD) have been established as

two distinct pathological entities, despite similarities in pathophysiology and demographics. Both diseases are neurodegenerative, chronic and progressive in nature, with irreversible neuronal cell loss being the key feature of both conditions. Furthermore, both POAG and AD disease primarily affect the elderly, with a strongly age-dependent incidence. The progressive debilitating course of both diseases already has tremendous implications on an aging population. A number of possible common mechanisms linking the two diseases have come to light in the past two decades and epidemiological studies have reported an increased comorbidity with glaucoma and AD.

However, larger studies using accepted standardized criteria for the diagnosis of glaucoma are still needed to truly establish whether or not patients with AD are more likely to have glaucoma than non-AD subjects, and vice versa. Collectively, some studies suggest that patients with AD are perhaps two to four times more likely to have glaucoma, but this is partially negated by studies that found no increased risk of AD in glaucoma patients. It could be that patients with glaucoma do not have an increased risk of developing AD, but, by contrast, AD is a risk factor for the development of glaucoma, particularly normal tension glaucoma (NTG). The neurodegenerative changes of AD may result in the neurodegenerative changes of glaucoma, thus resulting in glaucomatous damage even without the presence of raised intraocular pressure (IOP).

Potential comorbidities of Glaucoma including hypertension, heart failure, hyperlipidemia, diabetes, airways disease and depression

Glaucoma is a frequent ophthalmologic condition leading to chronic progressive optic neuropathy, which can result in visual impairment and blindness. In addition, glaucoma is associated with a dysregulation of circadian rhythms, as well as with a high incidence of sleep disorders, depression, and anxiety. Recently, there has been evidence for a progressive loss of intrinsically photosensitive retinal ganglion cells (ipRGC) because of oxidative stress in glaucoma. As ipRGC are responsible for the photic transduction to the circadian system and subsequent melatonin secretion, and melatonin is involved in the pathophysiology of circadian desynchronization, sleep disorder, and depression, an impairment of photodependent melatonergic signaling may be a common pathway connecting glaucoma with these comorbidities.
In a retrospective, nationwide, case-control study using an administrative database in Taiwan more than half (50.5%) of the OAG patients had hypertension, and more than 30% had hyperlipidemia or diabetes (30.5% and 30.2%, respectively). The prevalences of 28 of 31 comorbidities were significantly higher for OAG patients than subjects without glaucoma after adjusting for age, gender, urbanization level, and monthly income. The adjusted odds ratio was more than 1.50 for hypertension, hyperlipidemia, systemic lupus erythematosus, diabetes, hypothyroidism, fluid and electrolyte disorders, depression, and psychosis. Among the studied comorbidities, the prevalence difference of the OAG group minus the control group was 3% or higher for hypertension, hyperlipidemia, stroke, diabetes, liver disease, and peptic ulcer. A study published in the British Journal of Ophthalmology also shows that having high blood pressure, it can also lead to glaucoma. In addition, inhaled steroids have been associated with the development of cataracts and while again these are much more likely to occur in patients on frequent or maintenance oral corticosteroids, they are frequent in patients attending severe asthma clinics. A meta-analysis demonstrated an increased risk of 25% for each 1,000µg per day increase in the dose of beclomethasone equivalent inhaled steroid dose. Glaucoma risk is also increased in asthma patients on oral steroids.

MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Safety from non- clinical studies	Relevance to human usage
Toxicity	
Single-dose toxicity **Bimatoprost** After single i.p. dose of 96 mg/kg of Bimatoprost to mice there were no significant findings concerning clinical observations, mortality, body weight or gross pathology. Similarly, i.v. doses of up to 3 mg/kg produced no adverse effects in mice. The dose of 3 mg/kg represents a dose 1000 times higher than systemic human exposure assuming an ocular dose of one drop BID of 0.1% ophthalmic solution is given in humans (Lumigan Scientific Discussion, 2004).	Unrelated
Repeated-dose toxicity **Bimatoprost/Timolol Combination** Repeat-dose toxicity studies performed in rabbits and monkeys compared the findings made after ocular administration of bimatoprost 0.03% and timolol 0.5% as single-therapies with the findings made in the Ganfort® treatment group. The only treatment related effect seen in the one-month rabbit study was ocular discomfort in rabbits treated with timolol, whereas no treatment-related findings were made in a three-month rabbit study. The key findings made in a six-month monkey study included increased iridial pigmentation in the bimatoprost treatment group during weeks 4, 13, and 26. An increase in iridial pigmentation was also noted at week 26 in monkeys treated with Ganfort®, thus iridial pigmentation was delayed in monkeys treated with Ganfort® when compared to bimatoprost as a single-therapy. **Bimatoprost** In mice, toxicity of orally administered Bimatoprost was assessed in studies of 2 week, 4 weeks and 13 weeks duration. In the 4-week study, the only observed possibly treatment-related change was a tendency toward haemoconcentration. In the 13-week study, medullary lymphoid proliferation in the thymus, acute inflammatory cells in the superficial layers of the vagina and increased numbers of corpora lutea were detected. Thymic changes had regressed after the recovery period, and the vaginal changes had partially regressed. In rats, toxicity of orally administered Bimatoprost was evaluated in rats in 2-week studies, 4 weeks, 13 weeks, and a 1-	Unrelated

Safety from non- clinical studies	Relevance to human usage
Toxicity	
year study. In the two-week studies, the high dose of 16 mg/kg/day produced drug related testicular changes of bilateral degeneration of the testis and increased abnormal germ cells in the tubular lumen of the epididymis. An increase in vacuolization of the cortical cells in the adrenal glands was also present among animals in all Bimatoprost treated groups. In the 13-week study, decreased bodyweight and mildly increased serum enzymes were observed. The changes reversed after the recovery period of 4 weeks. Ovarian weight was increased in females at all dosages, and was accompanied by microscopic findings of increased numbers of prominent, vacuolated corpora lutea at all dosages. The ovarian weight increase was reversible. Statistically significantly lower epididymis weights were noted for males receiving 16 mg/kg/day. In the one year study, treatment related microscopic pathological findings were cellular vacuolation in corpora lutea of the ovaries observed at termination, with partial reversibility at 8 weeks. The toxicity of intravenously administered Bimatoprost was evaluated in studies of 1, 2 and 4 week's duration in rats. In a one-week study, there were no treatment-related deaths. Clinical signs of deceased motor activity, dyspnoea, cyanotic tail and soft stool were observed. In the high dose group, animals additionally showed signs of ataxia, gasping, ptosis, lethargy, and piloerection. Mean body weights were decreased in the 50 and 100 mg/kg dose groups and there were numerous changes in blood chemistry parameters. In the 4 week study, vacuolated corpora lutea were found in females. Toxicokinetic measurements showed that Bimatoprost was rapidly eliminated from blood and the animals were exposed to steady-state concentrations throughout the study. The AUCde values in the rat studies ranged from 2.5 to 4100 folds greater than the values in humans given the clinical regimen. The ocular studies in rabbits were of 3 days, 1 month, and 6 months duration. In these studies, the main findings were transient slight conjunctival hyperaemia, transient slight ocular discomfort, but no systemic or corneal toxicity was observed. In dogs, after topical administration of Bimatoprost, slight ocular discomfort, transient slight hyperaemia and miosis were observed. Miosis was noted to be an expected dog-specific pharmacological effect. The transient ocular discomfort and conjunctival hyperaemia observed in some rabbit and dog studies were believed to be connected to more frequent dosing in these cases. Ocular sensitivity additionally appeared to be related to	

Safety from non- clinical studies	Relevance to human usage
Toxicity	
vehicle administration (Lumigan Scientific Discussion, 2004). It should be noted that similar ocular effects were not observed in monkeys. In a 52 week study, monkeys were administered topical Bimatoprost once or twice daily. Increased iridial pigmentation was observed in all drug–treated groups at week 13 and during the remainder of the study. The incidence of increased pigmentation was associated with the frequency of dosing. The increased iridial pigmentation did not reverse after treatment cessation. At week 26 to 35, periocular effects, characterised by a prominent upper and/or lower sulcus, resulting in a widening of the palpebral fissure of the treated eye, were observed in all drug-treated groups. Periocular effects completely resolved by the end of the recovery period. Since iridial pigmentation and It should be noted that similar ocular effects were not observed in monkeys. In a 52 week study, monkeys were administered topical Bimatoprost once or twice daily. Increased iridial pigmentation was observed in all drug–treated groups at week 13 and during the remainder of the study. The incidence of increased pigmentation was associated with the frequency of dosing. The increased iridial pigmentation did not reverse after treatment cessation. At week 26 to 35, periocular effects, characterised by a prominent upper and/or lower sulcus, resulting in a widening of the palpebral fissure of the treated eye, were observed in all drug-treated groups. Periocular effects completely resolved by the end of the recovery period. Since iridial pigmentation and widening of the palpebral fissure have been observed in monkeys with prostaglandin analogues, including latanoprost, these effects are likely related to this pharmacological class. When Bimatoprost was administered once daily by i.v. injection to male and female monkeys for 4 weeks, no local or systemic adverse effects were observed. In a 17-week i.v. study, similarly to the 1-year ocular study, a reversible increase in the prominence of the periocular sulci was observed in all drug-treated groups. These effects occurred after 9 weeks of treatment. No systemic effects occurred at any dose (Lumigan Scientific Discussion, 2004). Following the reports of eyelash growth during the treatment of glaucoma with Bimatoprost and other prostaglandin analogues (PGA), the effect of Bimatoprost among other PGA was studied in New Zealand white rabbits, which received daily topical application of Bimatoprost, tafluprost, travoprost and latanoprost in the left eye for 4 weeks. Results showed that Bimatoprost and tafluprost groups had significant increases in eyelash length. No	

Safety from non- clinical studies	Relevance to human usage
Toxicity	
significant eyelash growth in rabbits receiving travoprost and latanoprost was observed after 1 month of treatment (Giannico et al, 2013).	
Carcinogenicity **Bimatoprost** The originator submitted the results of two 104-day carcinogenicity studies, one in rats and one in mice, as part of the application for first line therapy. In both mice and rats, systemic absorption and exposure was demonstrated at oral dosing in the carcinogenicity studies. Exposure margins when compared to human dosing were large. The overall conclusion of the carcinogenicity studies in rats and mice was that there was no evidence of a tumorigenic potential of Bimatoprost (Lumigan Scientific Discussion, 2004). **Timolol** In a two-year oral study of timolol maleate in rats there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day (300 times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage; there were no clinically meaningful changes in serum prolactin.	Unrelated
Genotoxicity **Bimatoprost** The standard battery of genotoxicity tests showed no evidence of genotoxic potential. Bacterial reverse mutation assays in S.typhimurium and E. coli were negative. Similarly, the mouse lymphoma assay, mouse micronucleus assay as well as the mouse bone marrow micronucleus test all gave negative results. The results of these in vitro and in vivo mutagenicity tests indicate that Bimatoprost is not genotoxic (Lumigan Scientific Discussion, 2004). **Timolol** Timolol maleate was devoid of mutagenic potential when evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell	Unrelated

Safety from non- clinical studies	Relevance to human usage
Toxicity	
transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant ($p \leq 0.05$) elevations of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test (*Timoptol® SPC, 2014*).	
Reproductive toxicity **Bimatoprost** Reproductive toxicity studies were conducted in mice, rats and rabbits. However, the rabbit was precluded as a species to evaluate embryo-foetal developmental toxicity. In mice, maternal toxicity such as decreased number of pregnancies, abortions or resorptions was seen at doses of 0.3 mg/kg/day or higher. At the lowest-observed-adverse-effect-level (LOAEL) for maternal toxicity (0.3 mg/kg/day), the AUCde was 33 times higher than the AUCde in humans given the clinical regimen. At the embryo/foetal no-observed-adverse-effect-level (NOAEL) of 0.6 mg/kg/day, the AUCde was 72 times higher than in humans treated with the clinical regimen. In the studies in rats, as doses of 1.0 mg/kg/day or higher produced abortions, lower doses were chosen in the following studies for evaluation of dose-response relationships. In the definitive embryo/foetal toxicity study in pregnant female rats, localised alopecia and abortions were observed. The maternal NOAEL was 0.3 mg/kg/day. In the perinatal/postnatal development study in pregnant rats, no overt maternal toxicity was observed in any dosage group. At doses of 0.3 mg/kg/day or more, gestation and perinatal development was affected, in that gestation length was reduced, there were late resorptions and foetal death, postnatal mortality and reduced pup body weight. The different reproduction toxic effects seen in rats and the lack of foetuses for evaluation in rabbits may be related to the exaggerated pharmacological effect of Bimatoprost. Prostaglandin analogues are known to have profound effects on the female reproductive system of mammals. However, in vitro studies showed that Bimatoprost does not act through the PGF2α-sensitive (FP) receptor. In vitro studies also showed that where rabbit isolated uteri were extremely sensitive to Bimatoprost, isolated human and rodent myometrium were	Animal studies have shown reproductive toxicity at high maternotoxic doses

Safety from non- clinical studies	Relevance to human usage
Toxicity	
found to be unresponsive to Bimatoprost, indicating that bimatoprost sensitive receptors do not mediate uterine contractions in rodents and humans (Lumigan Scientific Discussion, 2004). However, the metabolite 17-phenyl trinor PGF2α (AGN 191522) does activate the classical FP receptor and induces contractions in isolated mouse, rat, and rabbit uteri and in human myometrium. The metabolite is found in considerable levels in mice, rats and rabbits. It is argued that humans do not produce this metabolite following ocular dosing, and therefore the reproduction toxicity risk would be negligible in humans treated ocularly. In the clinical trials, metabolism to 17-phenyl trinor PGF2α was not detected in women treated ocularly with Bimatoprost for 14 days, and Bimatoprost incubated in human blood also did not convert to this metabolite. It might therefore be that Bimatoprost poses no abortion risk in humans. The abortions seen in mice and rat studies may either reflect the non-selective activation of FP receptors because of high doses given or the selective activation by the metabolite 17-phenyl trinor PGF2α (Lumigan Scientific Discussion, 2004). **Timolol** Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose (*Timoptol® SPC, 2014*). Reproduction studies in mice, rats, and rabbits using oral timolol dosages up to 50 mg/kg daily (7000 times the systemic exposure following the maximum recommended human ophthalmic dosage) have not revealed evidence of harm to the fetus. Oral timolol dosages of 1 g/kg daily (142,000 times the systemic exposure following the maximum recommended human ophthalmic dosage) were maternotoxic and resulted in an increased number of fetal resorptions in mice. Increased fetal resorptions were also observed in rabbits receiving oral timolol dosages 14,000 times the systemic exposure following the maximum recommended human ophthalmic dosage.	

Safety from non-clinical studies	Relevance to human usage
General safety pharmacology	
Bimatoprost/timolol combination No safety pharmacology studies have been performed with Ganfort. Nevertheless the safety of bimatoprost and timolol is well	Safety and efficacy profile of bimatoprost and timolol in

characterized and there is nothing to indicate that drug interaction occurs (*Ganfort® Scientific Discussion, 2006).* **Bimatoprost** Based on safety studies performed in rats and conscious dogs, bimatoprost is not expected to exert any effect on blood pressure, heart rate, electrocardiogram, or respiration rate. Bimatoprost showed no effect in general activity and behaviour tests and in tests on CNS performed in mice and rats. Bimatoprost exhibited only very low activity in the urinary excretion and digestive system. An ocular surface hyperaemic response was observed during chronic bimatoprost treatment but was not associated with inflammation (Ganfort® Scientific Discussion, 2006*).* **Timolol** In humans, topical non-selective β-blockers are associated with mild ocular side effects that include ocular irritation and conjunctival hyperaemia. Timolol maleate 0.5% administered topically or intravenously, decreased basal blood pressure and heart rate of anaesthetised dogs. Timolol may be extensively absorbed systemically after ocular inoculation thus it is contraindicated in patients with bronchial asthma or severe chronic obstructive pulmonary disease, and serious systemic effects such as bradycardia, second- and third-degree atrioventricular block, overt cardiac failure and cardiogenic shock. Timolol may be extensively absorbed systemically after ocular inoculation and therefore specific warnings are given in the SPC on the adverse reactions that can be seen after administration of β-blockers. Furthermore, under 4.3 in the SPC, Ganfort is contraindicated in patients with reactive airway disease, sinus bradycardia, second- and third-degree atrioventricular block, overt cardiac failure, cardiogenic shock and patients hypersensitive to the active ingredients or any of the excipients (*Ganfort® Scientific Discussion, 2006).*	humans has been demonstrated
Mechanisms for drug interactions	
No interaction studies have been performed with the bimatoprost/timolol combination	Unrelated
References of module SII	Lumigan Scientific Discussion, 2004 Ganfort® Scientific Discussion, 2006 Timoptol® SPC, 2014 Module 2.4 - Non-clinical Overview

SII CONCLUSIONS ON NON-CLINICAL DATA

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Bimatoprost/timolol combination

Repeated dose ocular toxicity studies on bimatoprost/timolol showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol

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

Therefore, no significant risk for human safety is expected with therapeutic doses of bimatoprost/timolol eye drops solution.

MODULE SIII: CLINICAL TRIAL EXPOSURE

SIII.1 BRIEF OVERVIEW OF DEVELOPMENT

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative free eye drops, solution' is a generic formulation of *Ganfort® (Allergan)*. This is being a 'hybrid' application under the Article 10(3) of European Directive 2001/83/EC. Formulations of bimatoprost/timolol have been well established in Europe for more than a decade.

SIII.2 CLINICAL TRIAL EXPOSURE

Four clinical randomised, double-masked, parallel studies have been conducted to evaluate the efficacy and safety of the bimatoprost 0.03% /timolol 0.5 % combination ophthalmic solution [Ganfort] in patients with open angle glaucoma or ocular hypertension.

Two 12-months superiority studies of similar design compared the Ganfort combination with the individual components applied as monotherapy. The Ganfort combination was also compared to each monotherapy in a superiority study of 12 weeks duration. A non-inferiority study compared the Ganfort combination with the adjunctive application of bimatoprost and timolol, and with bimatoprost monotherapy for internal validation, in a 3 weeks trial. The Ganfort combination was dosed once daily in the morning, bimatoprost was dosed once daily in the evening, and timolol was dosed twice daily (morning and evening with an interval of approximately 12 hours), consistent with the approved regimen.

In none of the superiority trials was a consistent statistically significant difference between the Ganfort combination and bimatoprost seen for the chosen primary endpoint. The applicant has provided responder analyses addressing the scientifically and clinically accepted important parameters namely the percentage of patients achieving IOP control < 18 mm Hg, and a decrease in diurnal IOP from baseline > 20 %. These analyses were performed for the overall population and the subpopulation of patients inadequately controlled on prostaglandins/prostamides. This subpopulation encompasses around one third of the study population, namely 373/1061 patients. The difference in the incidence of patients achieving >20 % decrease in diurnal IOP from baseline is clinically and statistically significantly superior in favour of the bimatoprost/timolol combination group versus the bimatoprost group for both populations. As for the analysis in the incidence of patients achieving IOP < 18 m m Hg at all follow-up visits the difference between the Ganfort combination and the monotherapy group is statistically significant in the analysed subpopulation and clearly numerically different in the overall population in favour of the Ganfort combination. Thus, results from this important subpopulation of patients inadequately controlled on prostaglandins/prostamides, support a better effect of the Ganfort combination therapy than of bimatoprost alone. Considering the results of study 192024-504T that addresses only patients not responsive to β-blocker therapy the full picture of efficacy in the proposed therapeutic indication is justified.

In study 504T a numerically superior effect was not found at all observation points. A statistically superior effect was observed for the Ganfort combination over timolol 0.5 %. In the non-inferiority study against the concurrent regimen, proof of non-inferiority was not found obeying

the all the predefined criteria, which were, admittedly, demanding. The achieved differences were, however, within the standard criteria for non-inferiority of 1.5 mm Hg.
The long-term safety population evaluated under controlled conditions is considered sufficient to assess a favourable safety profile for the Ganfort combination.

The overall efficacy of the bimatoprost 0.03 %/timolol 0.5 % eye drops combination in the treatment of patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to β-blocker alone should be assessed in connection with the better safety profile, which is primarily reflected in a lower frequency of adverse reactions and a lower withdrawal rate because of adverse events (Ganfort Scientific discussion, EMEA 2006).

MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 LIMITATIONS OF ADR DETECTION COMMON TO CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Not applicable.

SIV.2 EFFECT OF EXCLUSION CRITERIA IN THE CLINICAL TRIAL DEVELOPMENT PLAN

Not applicable.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Special populations, included in the table below, have not been studied in clinical trials. Therefore for these populations bimatoprost/timolol should be either used with caution or it is not recommended.

Special Population	
Patients with renal and hepatic impairment	Bimatoprost/timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.
Pregnancy	There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. [Invented name] should not be used during pregnancy unless clearly necessary. **Bimatoprost** No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses. **Timolol** Epidemiological studies have not revealed malformative effects but 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 [Invented name] is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice.
Breastfeeding	**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. **Bimatoprost** It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. [Invented name] should not be used by breast-feeding women. <u>Fertility</u> There are no data on the effects of bimatoprost/timolol on human fertility.
Paediatric patients	The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.
Bimatoprost/timolol use in patients with inflammatory ocular conditions	Bimatoprost/timolol has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

SIV.4 CONCLUSIONS ON THE POPULATIONS NOT-STUDIED AND OTHER LIMITATIONS OF THE CLINICAL TRIAL DEVELOPMENT PROGRAMME

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Safety concern	Comment	Yes/No
Paediatric patients	NA	Yes
Use during pregnancy and lactation	NA	Yes

MODULE SV - POST-AUTHORISATION EXPERIENCE

Since there are no safety concerns regarding safety and efficacy of *[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'* based on the post marketing experience, no post-authorisation efficacy studies were completed or are planned to be conducted.

SV.1 ACTION TAKEN BY REGULATORY AUTHORITIES AND/OR MARKETING AUTHORISATION HOLDERS FOR SAFETY REASONS

Not applicable.

SV.2 NON-STUDY POST-AUTHORISATION EXPOSURE

Not applicable.

SV.3 POST-AUTHORISATION USE IN POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Not applicable.

SV.4 POST-AUTHORISATION OFF-LABEL USE

Not applicable.

SV.5 EPIDEMIOLOGICAL STUDY EXPOSURE

Not applicable.

MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution' is a generic formulation of *Ganfort® eye drops, solution (Allergan).*

SVI.1 POTENTIAL FOR HARM FROM OVERDOSE

The SPC of the product clearly indicates the posology of the active substance. Because of the nature of these medications, overdose is extremely uncommon. The volume of liquid contained in one eye drop varies with the thickness of the solution, the design of the dropper and the way in which the patient uses the dropper to dispense drops. Bimatoprost/timolol preservative-free eye drops solution is contained in a white opaque LDPE bottle and white Novelia nozzle (HDPE and silicone) with a blue tip and sealed with a white HDPE cap.
The container supports two general functions:

- Sealing of the container and protection of the content during storage and transportation.
- Delivery of a metered dose of the pharmaceutical formulation so that the potential for overdosage is minimized.

The specific pharmaceutical product is subject to medical prescription. Therefore there is no place for potential for overdose, since the patient follows the physician's instructions.

SVI.2 POTENTIAL FOR TRANSMISSION OF INFECTIOUS AGENTS

There is no potential for transmission for infectious agents, since the product is manufactured according to the EU guidelines that determine Good Manufacturing Practices. In addition, active substances as well as excipients used in the manufacturing of product are in accordance with the European Union *'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)'*

However, patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. To prevent contamination of the plug applicator and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the plug applicator of the bottle. Patients should be informed of the correct handling of the ophthalmic clearly described in the section 4.2 of the SPC and in the PL of the product.

SVI.3 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The indications of the medicinal product are clearly mentioned in section 4.1 of the SPC. The medicinal product is subject to medical prescription and in the PL of the product it is clearly referred that the medicine has been prescribed for a specific patient and must not be passed to others. However, bimatoprost/timolol belongs to 'Ophthalmological, beta-blocking agents' pharmacotherapeutic group (ATC code: S01ED51). Thus, if more than one topical ophthalmic medicinal product should be used, the medicinal products must be administered at least 5 minutes apart.

However, based on the established long term use of prostaglandins analogues as well as the beta blockers and their well registered adverse events, the consequences of misuse for illegal purposes are not expected to deviate from known adverse events.

SVI.4 POTENTIAL FOR MEDICATION ERRORS

Please note that there is limited potential for medication errors. There are no literature findings that have resulted from medication errors.

The indications of the medicinal product are clearly mentioned in section 4.1 of the SPC and section 1 of PL.

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution' is subject to medical prescription and in the PL of the product it is clearly mentioned that the medicine has been prescribed for a specific patient and must not be passed on to others.
Bimatoprost penetrates the human cornea and sclera well in vitro. After ocular administration, the systemic exposure of bimatoprost is very low, with no accumulation over time. After timolol ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/mL in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

Therefore, there is not potential for serious harm if the product is administered to the wrong patient.

SVI.5 POTENTIAL FOR OFF-LABEL USE

The medicinal product is subject to medical prescription and in the PL of the product it is clearly referred that the medicine has been prescribed for a specific patient and must not be passed to others.

[Bimatoprost/timolol] is used for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

In December 2008, bimatoprost ophthalmic solution 0.03% was approved in the United States for the treatment of hypotrichosis of the eyelashes. In a double-blinded, randomized, vehicle-controlled trial, bimatoprost safely and effectively grew natural eyelashes, making them longer, thicker, and darker. However, this use of bimatoprost is not licensed in the EU.

The ability of prostaglandin analogs to increase eyelash growth does not appear limited to bimatoprost. Published reports describe latanoprost and travoprost, both prostaglandin analogs used to treat ocular hypertension, as being associated with eyelash changes, including increases in length and darkness. The use of prostaglandin analogues or prostamides as cosmetic eyelash enhancers is becoming more popular. Healthcare professionals should advise that all prescription-

only medicines should only be used under medical supervision. This advice is even more applicable when prescription-only medicines are used outside their licensed indications.

SVI.6 SPECIFIC PAEDIATRIC ISSUES

The SPC of the product clearly states in section 4.2 that the safety and efficacy of *'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'* in paediatric patients have not been established. Therefore *'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'* use is not recommended in in children aged 0 to 18 years.

SVI.7 CONCLUSIONS

Safety concerns from this module (to be carried through to Part II Module SVIII)	
Safety concern	Comment
Off-label use (cosmetic use for stimulation of eyelash growth)	Healthcare professionals should advise that all prescription-only medicines should only be used under medical supervision; consequently off-label use of bimatoprost/timolol should be discouraged.

MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F2_{\alpha}$ ($PGF2_{\alpha}$) that does not act through any known prostaglandin receptors.
Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

SVII.1 NEWLY IDENTIFIED SAFETY CONCERNS (SINCE THIS MODULE WAS LAST SUBMITTED)

Not applicable.

SVII.2 RECENT STUDY REPORTS WITH IMPLICATIONS FOR SAFETY CONCERNS

Not applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED AND POTENTIAL RISKS FROM CLINICAL DEVELOPMENT AND POST-AUTHORISATION EXPERIENCE (INCLUDING NEWLY IDENTIFIED)

Important Identified Risk	
Hyperpigmentation	
Frequency with 95 % CI	Uncommon (≥1/1,000 to <1/100)
Seriousness/outcomes	Although a final assessment of the clinical significance of prostaglandin-induced iris pigmentation currently is impossible to make, it appears that the only clear-cut disadvantage is a potential heterochromia between the eyes in unilaterally treated patients because the heterochromia is likely to be permanent, or very slowly reversible.
Severity and nature of risk	Adverse event. After discontinuation of therapy, no further increase in brown iris pigment has been observed. All existing data to date support that these changes are solely cosmetic in nature, and have not posed a health risk in any form
Background incidence/prevalence	After 12 months treatment with bimatoprost/timolol, the incidence of iris pigmentation was 0.2%. After 12 months

Important Identified Risk	
Hyperpigmentation	
	treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment.
Risk groups or risk factors	Adverse event that may occur in all patients. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes.
Potential mechanisms	Bimatoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes.
Preventability	Not applicable.
Impact on individual patient	After discontinuation of therapy, no further increase in brown iris pigment has been observed.
Potential public health impact of safety concern	All existing data to date support that these changes are solely cosmetic in nature, and have not posed a health risk in any form.
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Pr LUMIGAN® RC – product Monograph. Allergan Inc. Revised September 10, 2009 Johan W Stjernschantz, MD, PhD, Daniel M Albert, MD, Dan-Ning Hu, MD, Filippo Drago, MD, PhD, Per J Wistrand, MD, PhD. Mechanism and Clinical Significance of Prostaglandin-Induced Iris Pigmentation. Survey of Ophthalmology Volume 47, Supplement 1, August 2002, Pages S162–S175.
MedDRA terms	Iris hyperpigmentation

Important Identified Risk	
Macular oedema	
Frequency with 95 % CI	Not known
Seriousness/outcomes	Macular edema occurs when fluid and protein deposits collect on or under the macula of the eye (a yellow central area of the retina) and causes it to thicken and swell (edema). The swelling may distort a person's central vision, as the macula is near the center of the retina at the back of the eyeball. This area holds tightly packed cones that provide sharp, clear central vision to enable a person to see detail, form, and color that is directly in the direction of gaze.
Severity and nature of risk	Possible adverse event. Vision loss may be mild to severe, but in many cases, peripheral (side) vision remains.

Important Identified Risk	
Macular oedema	
Background incidence/prevalence	Can not be determined. Adverse event identified from post-marketing experience. As this adverse event was reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely.
Risk groups or risk factors	Macular edema can occur as a rare side effect in eyes treated with bimatoprost or other prostaglandin analogues. Pseudophakic eyes and eyes with other risk factors for macular edema are most likely to be affected, and phakic eyes without risk factors may not be at risk.
Potential mechanisms	The mechanisms associated with prostaglandins (PG)-induced intraocular inflammation have not been completely elucidated. It has been suggested that PGF2a stimulates the release of PGE2, which in turn stimulates the release of arachidonic acid by activating phospholipase II. Arachidonic acid may promote the increase of eicosanoids as well as other proinflammatory mediators in the eye, ultimately leading to changes in the blood–aqueous and blood–retinal barriers
Preventability	The edema resolves, and visual acuity returns, upon cessation of prostaglandin therapy.
Impact on individual patient	Deterioration of patient quality of life due to vision loss.
Potential public health impact of safety concern	Pseudophakic eyes and eyes with other risk factors for macular edema are most likely to be affected, and phakic eyes without risk factors may not be at risk. However, discontinuation of treatment in all populations (at risk or not) should be immediate.
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24 Faruk Oztürk MD, Güliz Fatma Yavas MD, Tuncay Küsbeci MD. The Effect of Ocular Hypotensive Agents on Macula. Annals of Ophthalmology October 2007, Volume 39, Issue 4, pp 302-306 ES Arcieri, PTP Pierre Filho, TH Wakamatsu and VP Costa. The effects of prostaglandin analogues on the blood aqueous barrier and corneal thickness of phakic patients with primary open-angle glaucoma and ocular hypertension. Eye (2008) 22, 179–183
MedDRA terms	cystoid macular oedema

Important Identified Risk	
Respiratory disorders	
Frequency with 95 % CI	Uncommon (>1/1,000 to ≤1/100)
Seriousness/outcomes	Bimatoprost did not significantly alter mean respiratory rate due to a relatively rapid elimination half-life. However, timolol may induce a decrease in the forced expiratory volume. Constriction of the air passages of the lung (as in asthma) by spasmodic contraction of the bronchial muscles. The severity of bronchoconstrictor response is not predictable
Severity and nature of risk	The results of a physician survey from 2002 revealed that systemic events were reported in 10% of bimatoprost-treated patients, 4% of latanoprost-treated patients and 1-5% of those treated with travoprost. The most common events noted were colds, flu and upper respiratory tract infections. Not all of the comparative trials reported systemic adverse events experienced by the study population. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Respiratory failure, dyspnoea, cough have also been reported.
Background incidence/prevalence	Can not be determined. For latanoprost upper respiratory tract infection the rate was of approximately 4% in clinical trials. Between September 1978 and December 1985, 450 case reports of serious respiratory and cardiovascular events and 32 case reports of death attributed to ophthalmic timolol were received by the United States Food and Drug Administration and the National Registry of Drug-Induced Ocular Side Effects. Two hundred sixty-seven patients (55%) experienced a cardiac arrhythmia or a bronchospasm-related event. The median age was 68 years (n = 365). Fifty-five percent of the patients were women and 45% were men (n = 41). Of the 212 persons for whom medical history was provided, 129 (61%) had respiratory disease, 65 (31%) had cardiovascular disease, 13 (6%) had other illnesses, and five (2%) had no underlying illness. Of the 318 patients for whom data on duration of drug use were available 106 (33%) experienced their adverse event within one week of beginning timolol therapy: 73 (23%) had their events on the first day of therapy. Of 192 patients for whom information was available 177 (92%) improved after the drug was discontinued.
Risk groups or risk factors	Patients with COPD, asthma or compromised respiratory

Important Identified Risk	
Respiratory disorders	
	function due to other conditions should be treated with caution.
Potential mechanisms	Prostaglandins elicit contractile responses in isolated human bronchial smooth muscle with bronchial hyperresponsiveness and constriction, and changes in microvascular leakage airway smooth muscle. Beta-blockers antagonise the effects of sympathetic nerve stimulation or circulating catecholamines at beta-adrenoceptors which are widely distributed throughout body systems. Beta1-receptors are predominant in the heart (and kidney) while beta2-receptors are predominant in other organs such as the lung, peripheral blood vessels and skeletal muscle. Bronchospasm in susceptible individuals due to blockade of beta2-receptors which mediate dilation in the bronchi
Preventability	Patients with mild/moderate COPD, asthma or compromised respiratory function due to other conditions should be treated with caution. In addition bimatoprost/timolol is contraindicated in patients with reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
Impact on individual patient	Potential adverse events: *Timolol:* Cough *Combination:* rhinitis, dyspnoea, bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Potential public health impact of safety concern	Potentially life threatening
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24 Anne J Lee and Peter McCluskey. Clinical utility and differential effects of prostaglandin analogs in the management of raised intraocular pressure and ocular hypertension. Clin Ophthalmol. 2010; 4: 741–764 M. Detry-Morel. Side effects of glaucoma. Bull. Soc. Belge Ophtalmol., 299, 27-40, 2006. Marjo Volotinen, Expression of cytochrome P450-enzymes

Important Identified Risk	
Respiratory disorders	
	and metabolism of timolol in human ocular tissue, Academic dissertation Usama Jihad Abdul Qader, Nawar Abdul Jaleel Turkey, Topical TIMOLOL side effects(patient's awareness, prevention) , prescription, and pretreatment assessment, Tikrit Medical Journal 2010; 16(2)150-155 Nelson WL, Fraunfelder FT, Sills JM, Arrowsmith JB, Kuritsky JN, Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985., Am J Ophthalmol. 1986 Nov 15; 102(5):606-11.
MedDRA terms	Rhinitis, dyspnoea, bronchospasm, cough

Important Identified Risk	
Choroidal detachment	
Frequency with 95 % CI	Not known
Seriousness/outcomes	Choroidal detachment has been reported with administration of aqueous suppressant therapy after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.
Severity and nature of risk	Choroidal detachment is an ocular adverse event related to timolol.
Background incidence/prevalence	Cannot be determined. Adverse event reported either from clinical trials or been reported during product use in clinical practise. As these adverse events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely.
Risk groups or risk factors	Patients with history of ocular surgery or pre-existing chronic corneal defects, in particular concomitantly treated with timolol.
Potential mechanisms	Ciliochoroidal detachments occur under a variety of pathological circumstances and are most commonly noted following intraocular surgery where hypotony is combined with postoperative inflammation. Although the condition is easily recognized, the pathophysiologic mechanisms involved are not well understood. Recent intraocular surgery is the most common association. Eye trauma and corneal ulcers are frequent, and panretinal photocoagulation can also cause choroidal detachments. The use of IOP-lowering medications has also reportedly been

Important Identified Risk	
Choroidal detachment	
	associated with serous choroidal detachments.
Preventability	Caution should be made in patients at risk.
Impact on individual patient	Serious choroidal detachment can result in phthisis/ptosis, retinal detachment, cataract formulation, or intractable secondary glaucoma.
Potential public health impact of safety concern	Morbidity in serious choroidal detachment is significant. In phakic eyes, lens opacities can progress rapidly. Cyclitic pupillary membranes may develop. When a flat chamber is present, corneal endothelial damage and peripheral anterior synechiae can occur. Chronic choroidal detachment can lead to maculopathy and globe phthisis. In hemorrhagic detachment, morbidity is the same as for serous detachment, but the prognosis is worse. Loss of useful vision is reported in up to 40% of cases.
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Deniz Turgut Coban, Muhammet Kazim Erol, Ozgur Yucel. Hemorrhagic choroidal detachment after use of anti-glaucomatous eye drops: case report. Arq Bras Oftalmol. 2013;76(5): 309-10 Chapter 54e. Glaucoma associated with retinal disorders and retinal surgery. Sharma T, Salmon JF. Hypotony and choroidal detachment as a complication of topical combined timolol and dorzolamide. J Ocul Pharmacol Ther. Apr 2007; 23(2):202-5.
MedDRA terms	Choroidal detachment

Important Identified Risk	
Hypoglycaemia/diabetes	
Frequency with 95 % CI	Not determined
Seriousness/outcomes	Disease related concern. Related to systemic absorption of the drug.
Severity and nature of risk	Beta-adrenergic receptor blocking agents may mask symptoms of hypoglycaemia such as tremors, tachycardia and blood pressure changes. In addition, the nonselective beta-blockers (e.g., propranolol, pindolol, timolol) may inhibit catecholamine mediated glycogenolysis, thereby potentiating insulin-induced hypoglycaemia and delaying the recovery of normal blood glucose levels. Since cardioselectivity is not absolute, larger doses of beta-1

Important Identified Risk	
Hypoglycaemia/diabetes	
	selective agents may demonstrate these effects as well.
Background incidence/prevalence	Hypoglycaemia is a known adverse event but frequency cannot be estimated from the available data. Therapy with beta-blockers should be administered cautiously in patients with diabetes or predisposed to spontaneous hypoglycaemia *(incidence related to timolol remains unknown)*.
Risk groups or risk factors	Patients subject to spontaneous hypoglycaemia or to patients with labile diabetes
Potential mechanisms	Blockage of catecholamine actions by beta blockers can mask symptoms of hypoglycaemia (tremors, sweating, palpitations) that are all sympathetic system mediated. On the other hands, beta blockers inhibit gluconeogenesis in the liver and can thus potentate hypoglycaemia.
Preventability	In patients with group of risk particular attention should be given during treatment with timolol
Impact on individual patient	Potential life threatening condition
Potential public health impact of safety concern	Short term consequences of hypoglycaemia: seizures, coma, and death require hospitalisation usually in the intensive care unit
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Timolol disease interactions—Drug information on line Usama Jihad Abdul Qader, Nawar Abdul Jaleel Turkey, Topical TIMOLOL side effects(patient's awareness, prevention), prescription, and pretreatment assessment, Tikrit Medical Journal 2010; 16(2)150-155
MedDRA terms	Hypoglycaemia, Blood glucose decreased

Important Identified Risk	
Cardiac and vascular disorders	
Frequency with 95 % CI	Uncommon (>1/1,000 to ≤1/100)
Seriousness/outcomes	Adverse events related to the systemic absorption of the product. Beta-blockers related effects.
Severity and nature of risk	Adverse events, related to systemic absorption of the drugs. 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 therapy with other active substances should be considered. Patients with cardiovascular diseases should be

Important Identified Risk	
Cardiac and vascular disorders	
	watched 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.
Background incidence/prevalence	Can not be determined. Adverse event reported either from clinical trials or been reported during product use in clinical practice.
Risk groups or risk factors	Elderly and patients with cardiac, respiratory or neurological disease.
Potential mechanisms	Possibly by stimulation of prostaglandin F (FP) receptor outside the eye. In addition, in cardiac tissues, beta blockade causes a reduction in inotropic as well as chronotropic activity, which may further depress cardiac output and blood pressure in patients with peripheral circulatory disorders
Preventability	In elderly and patients with cardiac, respiratory or neurological disease that may be induced or exacerbated by topical ophthalmic agents' use of bimatoprost alone, timolol alone or their combination should be considered.
Impact on individual patient	Increased risk in patient with cardiac, respiratory or neurological disease
Potential public health impact of safety concern	Potentially life-threatening emergency requiring prompt treatment
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Alm A. Prostaglandin derivates as ocular hypotensive agents. Prog Retin Eye Res. 1998 Jul;17(3):291-312. Mr Jeremy P. Diamond. Systemic Adverse Effects of Topical Ophthalmic Agents. Drugs & Aging. November 1997, Volume 11, Issue 5, pp 352-360 W H Frishman. Beta-adrenergic receptor blockers. Adverse effects and drug interactions. Hypertension. 1988;11:II21 Meuche C, Heidrich H, Bleckmann H. [Raynaud syndrome following timolol-containing eyedrops]. Fortschr Ophthalmol. 1990; 87(1):45-7.
MedDRA terms	Atrioventricular block, cardiac arrest, arrhythmia, bradycardia, cardiac failure, congestive heart failure, chest pain, palpitations, oedema, hypotension, Raynaud's phenomenon, cold hands and feet.

Important Identified Risk	
Corneal toxicity – dry eye	
Frequency with 95 % CI	Rare (≥1/10,000 to <1/1000)
Seriousness/outcomes	Topical intraocular pressure-lowering drugs must penetrate across the tissues of the eye to reach their therapeutic targets. Often, these tissues show the first signs and symptoms of drug toxicity and adverse effects. These include eyelid dermatitis, malpositions, lacrimal system scarring, ocular discomfort upon instillation, tear film instability, conjunctival inflammation, subconjunctival fibrosis, conjunctival epithelium changes, and corneal surface and endothelial impairment. For these reasons, ophthalmologists should evaluate the risks and benefits of ophthalmic medications before initiating therapy, identify the minimum dosages necessary to achieve a therapeutic benefit, and monitor patients for local and systemic adverse effects
Severity and nature of risk	Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), conjunctivitis, blepharitis, keratitis, dry eyes, decreased corneal sensitivity, blurred vision, and corneal erosion have been reported
Background incidence/prevalence	Cannot be determined. Adverse event reported either from clinical trials or been reported during product use in clinical practise. As these adverse events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely.
Risk groups or risk factors	Risk increased in patients with corneal diseases
Potential mechanisms	The detailed mechanism of inflammatory response and/or direct toxicity of eye drops has yet to be determined, but it may vary with the different classes of eye drops.
Preventability	Ophthalmologist evaluate the risks and benefits of ophthalmic medications before initiating therapy, identify the minimum dosages necessary to achieve a therapeutic benefit, and monitor patients for local and systemic adverse effects
Impact on individual patient	Deterioration of patient quality of life if treatment with long-term consequences (toxicity)
Potential public health impact of safety concern	The consequences of disorder may require treatment
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Herreras JM, Pastor JC, Calonge M, Asensio VM., Ocular surface alteration after long-term treatment with an antiglaucomatous drug. Ophthalmology. 1992 Jul;

Important Identified Risk	
Corneal toxicity – dry eye	
	99(7):1082-8. Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1; 28(4):267-82. M. Detry-Morel, Side effects of glaucoma medications Bull. Soc. Belge Ophtalmol., 299, 27-40, 2006.
MedDRA terms	corneal erosion, foreign body sensation, eye dryness, decreased corneal sensitivity

Important Identified Risk	
Hypersensitivity to any allergen	
Frequency with 95 % CI	Not determined
Seriousness/outcomes	Adverse reactions after administration of ophthalmic products have frequently been observed. These reactions can be provoked by both active principles and excipients. Different pathogenic mechanisms have been suggested for such reactions, including immunologic ones.
Severity and nature of risk	Anaphylaxis that may be severe.
Background incidence/prevalence	Cannot be determined.
Risk groups or risk factors	Risk increased in patients with history of atopy or a history of severe anaphylactic reaction to a variety of allergens.
Potential mechanisms	Anaphylactoid and anaphylactic reactions occurs via modulation of adenylate cyclase, which can influence release of anaphylactogenic mediators
Preventability	Ophthalmologist evaluates the risks and benefits of ophthalmic medications before initiating therapy. Risk reduction efforts should be considered for patients receiving β-blockers who are prone to experience anaphylaxis
Impact on individual patient	Patient may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.
Potential public health impact of safety concern	Potentially life-threatening
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC John H. Toogood. Beta-blocker therapy and the risk of anaphylaxis. CMAJ, VOL. 136, MAY 1, 1987 Dr David M. Lang. Anaphylactoid and Anaphylactic Reactions. Drug Safety, May 1995, Volume 12, Issue 5, pp

Important Identified Risk	
Hypersensitivity to any allergen	
	299-304 Ventura, M. T.; Viola, M.; Gaeta, F.; Di Leo, E.; Buquicchio, R.; Romano, A. Hypersensitivity Reactions to Ophthalmic Products. Current pharmaceutical design, Volume 12, Number 26, September 2006 , pp. 3401-3410(10)
MedDRA terms	Hypersensitivity, Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis

Important Identified Risk	
Masking hyperthyroidism signs	
Frequency with 95 % CI	Unknown
Seriousness/outcomes	Beta-adrenergic receptor blocking agents are used to alleviate symptoms of hyperthyroidism such as tachycardia, anxiety, tremor and heat intolerance. Thus, use of timolol eye drops, because of it systemic absorption, may mask hyperthyroidism symptoms.
Severity and nature of risk	Adverse systemic effect due to systemic absorption of the drug.
Background incidence/prevalence	Incidence related to timolol remains unknown
Risk groups or risk factors	Patients with hyperthyroidism
Potential mechanisms	Blockade of catecholamine actions by beta blockers can mask symptom of hyperthyroidism that are all sympathetic system mediated
Preventability	To minimize this risk, cessation of beta-blocker therapy, when necessary.
Impact on individual patient	Complications due to hyperthyroidism, such heart problems, brittle bones, thyrotoxic crisis, myasthenia gravis.
Potential public health impact of safety concern	Potentially life threatening if hyperthyroidism is not treated or is inadequately treated
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Timolol disease interactions—Drug information on line Usama Jihad Abdul Qader, Nawar Abdul Jaleel Turkey, Topical TIMOLOL side effects (patient's awareness, prevention), prescription, and pretreatment assessment, Tikrit Medical Journal 2010; 16(2)150-155
MedDRA terms	NA

Important Identified Risk	
Co-administration with adrenaline	
Frequency with 95 % CI	Not known
Seriousness/outcomes	Both the anesthesiologist and the ophthalmologist must be aware that eyedrops are readily absorbed through hyperemic incised conjunctivae. Although small in volume, these drops contain highly concentrated medication that can produce systemic results. Infants and elderly patients are most susceptible. Systemic effects can be minimized by using lower concentrations, limiting instillation to only one or two drops, and promptly occluding the nasolacrimal duct at the time of instillation.
Severity and nature of risk	*Timolol:* Timolol is a β-adrenergic receptor blocking drug administered as eyedrops to treat glaucoma. Systemic effects include bradycardia, hypotension, congestive heart failure, and exacerbation of asthma and myasthenia gravis.
Background incidence/prevalence	Cannot be determined.
Risk groups or risk factors	Cases of a surgical operation
Potential mechanisms	Betablocking ophthalmological preparations may block systemic beta-agonist effects
Preventability	The anaesthesiologist should be informed when the patient is receiving timolol.
Impact on individual patient	Co-administration of timolol with adrenaline result in additive hypotensive effect of adrenaline, which is more pronounced in patients with exfoliative glaucoma
Potential public health impact of safety concern	Potentially life-threatening
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Ohrström A, Kättström O. Interaction of timolol and adrenaline. Br J Ophthalmol 1981 Jan; 65(1):53-5. Thomas JV, Epstein DL. Study of the additive effect of timolol and epinephrine in lowering intraocular pressure. Br J Ophthalmol 1981 Sep; 65(9):596-602. Chapter 63: Anesthesia for Eye, Ear, Nose, and Throat Surgery
MedDRA terms	NA

Others risks related to the product

Important Potential Risk
Increase in intraocular pressure

Important Potential Risk	
Increase in intraocular pressure	
Frequency with 95 % CI	Not known
Seriousness/outcomes	There is a potential for the IOP-lowering effect of prostaglandin analogues (e.g. bimatoprost) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues.
Severity and nature of risk	Adverse event related to potential drug interaction.
Background incidence/prevalence	Occasional cases have been reported
Risk groups or risk factors	Not applicable.
Potential mechanisms	Latanoprost and bimatoprost produce a greater IOP reduction with single than multiple daily doses. Proposed hypotheses for this effect are reduction of the uveoscleral outflow, increase in episcleral venous pressure of short duration, development of subsensitivity at the FP receptor or intracellular pathways, compromise in the classic pathway, and it was also speculated that a twice daily regimen presents a dose beyond the dose-response curve, resulting in a consequently lower effect. The fact that the free acid of bimatoprost is a potent FP receptor agonist and enzymes in mammalian ocular tissues may hydrolyse bimatoprost to its free acid could account for the increase in IOP observed with the adjunctive use of bimatoprost and latanoprost.
Preventability	Patients using [bimatoprost/timolol] with other prostaglandin analogs should be monitored for changes to their intraocular pressure.
Impact on individual patient	High eye pressure can cause glaucoma and permanent vision loss in some individuals. However, some people can have ocular hypertension without developing any damage to their eyes or vision
Potential public health impact of safety concern	The combination of bimatoprost and latanoprost or other prostaglandin analogues should not be considered as a therapeutic option in POAG because of the paradoxical increase in IOP.
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC Herndon LW, Asrani SG, Williams GH, Challa P, Lee PP. Paradoxical intraocular pressure elevation after combined therapy with latanoprost and bimatoprost. Arch Ophthalmol. 2002 Jun;120(6):847-9. Doi LM, Melo LA Jr, Prata JA Jr. Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial. Br J Ophthalmol. 2005 May;89(5):547-9.

Important Potential Risk	
Increase in intraocular pressure	
MedDRA terms	Intraocular pressure increased

Important Potential Risk	
Off-label use (cosmetic use for stimulation of eyelash growth)	
Frequency with 95 % CI	Eyelash growth: Common (≥1/100 to <1/10)
Seriousness/outcomes	Bimatoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes.
Severity and nature of risk	Concern related to adverse effects.
Background incidence/prevalence	Increase of the length and thickness of the eyelashes (hypertrichosis), as well as darkening of the eyelashes occurs in all races. Reported frequency of eyelashes changes varies between zero and 25% for latanoprost, between 0.7% and 52% for travoprost, and between 3% and 36% for bimatoprost. But in the same population, and using identical criteria for the changes, in studies with a follow-up duration up to six months, the rate was similar for all these three $PGF_{2\alpha}$ analogues. Eyelash changes associated with the use of unoprostone seems to be similar to those observed with latanoprost. Through registered as a side effect, less that 1% of patients complain about hypertrichosis, and many patients in fact prefer the longer lashes, for cosmetic reasons. However, hypertrichosis can lead to complains if it is unilateral, in case of unilateral use of $PGF_{2\alpha}$ analogues. If the topically applied $PGF_{2\alpha}$ analogues use in contact with the eyelids and the malar region, hypertrichosis and hyperpigmentation of the vellus hairs can occur. Discontinuation of $PGF_{2\alpha}$ analogue treatment results in reversal of eyelash pigmentation and hypertrichosis after spontaneous shedding of the lashes or following epilation. As a rare eyelash alteration, poliosis has been described in chronic use of bimatoprost, latanoprost and travoprost.
Risk groups or risk factors	Adverse event that may occur in all patients.
Potential mechanisms	When prostaglandin and prostamide analogs interact with the prostanoid receptors in the hair follicle, this most likely stimulates the resting follicles (telogen phase) to growing follicles (anagen phase). Prostaglandin and prostamide analogs may also prolong the anagen phase of eyelashes, leading to an increase of eyelash length.
Preventability	Healthcare professionals should advise that all prescription-only medicines should only be used under medical supervision. This advice is even more applicable when

Important Potential Risk	
Off-label use (cosmetic use for stimulation of eyelash growth)	
	prescription-only medicines are used outside their licensed indications.
Impact on individual patient	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Patients must be advised that bimatoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension and should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events.
Potential public health impact of safety concern	Although increased lash length does not have particularly deleterious physicological effects on the patients, bimatoprost is associated with other adverse events, both topical and systemic. This drug must be used under medical supervision and its off-label use for cosmetic purposes should be discouraged.
Evidence source	*'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*- SmPC M.Y. Shaikh and Ali A. Bodla. Letter to the Editor: Hypertrichosis of the Eyelashes from Prostaglandin Analog Use: A Blessing or a Bother to the Patient?Journal of ocular pharmacology and therapeutics, Volume 22, Number 1, 2006 Holló G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf. 2007 Jan;6(1):45-52. G Holló - Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book) Law SK. Bimatoprost in the treatment of eyelash hypotrichosis. Clin Ophthalmol. 2010 Apr 26;4:349-58.
MedDRA terms	Growth of eyelashes

SVII.4 IDENTIFIED AND POTENTIAL INTERACTIONS

SVII.4.1 OVERVIEW OF POTENTIAL FOR INTERACTIONS

Interaction studies with other medicinal products and other forms of interation have not been performed with *'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'*.

SVII.4.2 IMPORTANT IDENTIFIED AND POTENTIAL INTERACTIONS

Drug-Drug Interactions

No specific interaction studies have been performed with the bimatoprost/timolol fixed combination.

In clinical studies, bimatoprost was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of interactions.

Concomitant use of [Bimatoprost] and antiglaucomatous agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

There is a potential for the IOP-lowering effect of prostaglandin analogues (e.g. [Bimatoprost]) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues.

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, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

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.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Drug-Lifestyle Interactions

Effects on the Ability to Drive and Use Machines
[Bimatoprost/timolol] has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

SVII.5 PHARMACOLOGICAL CLASS EFFECTS

SVII.5.1 PHARMACOLOGICAL CLASS RISKS ALREADY INCLUDED AS IMPORTANT IDENTIFIED OR POTENTIAL RISKS

According to WHO the following active substances are under the pharmacological class of prostaglandin analogues:

ATC code	Name
S01EE01	latanoprost
S01EE02	Unoprostone (not authorized in EU, outside of the scope of this RMP)
S01EE03	bimatoprost
S01EE04	travoprost
S01EE05	tafluprost

Iris hyperpigmentation and respiratory disorders are pharmacological class effects common to topical prostaglandin use.

According to WHO the following active substances are under the pharmacological class of beta-blockers:

ATC code	Name
S01ED02	betaxolol
S01ED03	levobunolol
S01ED04	metipranolol
S01ED05	carteolol
S01ED06	befunolol

Adverse drug reactions associated with the use of beta blockers include hypoglycaemia, systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis, choroidal detachment, cardiac and vascular disorders.

SVII.5.2 IMPORTANT PHARMACOLOGICAL CLASS EFFECTS NOT DISCUSSED ABOVE

Not applicable.

MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of safety concerns	
Important identified risks	• Hyperpigmentation • Macular oedema • Respiratory disorders • Choroidal detachment • Hypoglycaemia/diabetes • Cardiac and vascular disorders • Corneal toxicity – dry eye • Co-administration with adrenaline • Hypersensitivity to any allergen • Masking hyperthyroidism signs
Important potential risks	• Increase in intraocular pressure • Off-label use (cosmetic use for stimulation of eyelash growth)
Missing information	• Use during pregnancy and lactation • Paediatric use

PART III: PHARMACOVIGILANCE PLAN

Routine pharmacovigilance Activities

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution' is a generic formulation. Therefore, routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring. Process followed for *'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'* under Article 10(3) of European Directive 2001/83/EC, includes collection and medical evaluation of Individual Case Safety Reports (ICSRs), expedited reporting of adverse drug reactions (ADRs), regular signal detection and signal evaluation, weekly screening of the scientific literature for ADR reports, maintenance and administration of the global safety database, preparation and processing of safety reports (e.g PSURs, etc), maintenance of the pharmacovigilance quality management system and standardised processes to define and decide on adequate measures for crisis management and risk minimization.

No additional Pharmacovigilance activities are established.

III.1 SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

Summary of safety concerns and planned Pharmacovigilance actions are described below:

Hyperpigmentation		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Macular edema		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Respiratory disorders		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Choroidal detachment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Hypoglycaemia/diabetes		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Cardiac and vascular disorders		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Corneal toxicity – dry eye		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Co-administration with adrenaline		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Hypersensitivity to any allergen		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Masking hyperthyroidism signs		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Increase in intraocular pressure		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Off-label use (cosmetic use for stimulation of eyelash growth)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Use during pregnancy and lactation		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Paediatric use		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in

Paediatric use		
		risk-benefit balance that currently remains favourable

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

Not applicable.

III.3 STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

Not applicable.

III.4 DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

III.5 SUMMARY OF THE PHARMACOVIGILANCE PLAN

Not applicable.

PART IV: PLAN FOR POST-AUTHORISATION EFFICACY STUDIES

'[Bimatoprost/Timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution' is being an application under Article 10(3) of European Directive 2001/83/EC, as amended.

Since there are no indications that the efficacy of Bimatoprost/timolol may vary over time or between different target population sub-groups, no post-authorisation efficacy studies were completed or are planned to be conducted.

IV.1 TABLES OF POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

IV.2 SUMMARY OF POST AUTHORISATION EFFICACY DEVELOPMENT PLAN

Not applicable.

IV.3 SUMMARY OF COMPLETED POST AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES BY SAFETY CONCERN

The table below summarises the routine risk minimisation activities (if any) that are in place for each safety concern.

Important identified risk	
Safety concern	**Hyperpigmentation**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of hyperpigmentation is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and bimatoprost/timolol. Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of bimatoprost/timolol, pigmentation of iris may be permanent. After 12 months treatment with bimatoprost/timolol, the incidence of iris pigmentation was 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iridial pigmentation are not known. Iris color changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Important identified risk	
	Section 4.8: Bimatoprost/timolol Eye disorders: iris pigmentation (uncommon)
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Macular oedema**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of macular oedema is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** Macular oedema, including cystoid macular oedema, has been reported with bimatoprost/timolol. Therefore, [Invented name] should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy). [Invented name] should be used with caution in

Important identified risk	
	patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated. ***Section 4.8:*** Bimatoprost/timolol Eye disorders: cystoid macular oedema (not known)
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Respiratory disorders**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of respiratory disorders is already included in *sections 4.3, 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.3:*** Contraindications: Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease. ***Section 4.4:*** Respiratory reactions, including death due to bronchospasm in patients with asthma have

Important identified risk	
	been reported following administration of some ophthalmic beta-blockers. [Invented name] 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. ***Section 4.8:*** Bimatoprost/timolol Respiratory, thoracic and mediastinal disorders: Rhinitis (common), dyspnoea (uncommon), bronchospasm (predominantly in patients with pre-existing bronchospastic disease) (not known) Timolol Respiratory, thoracic and mediastinal disorders: Cough
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Choroidal detachment**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of choroidal detachment is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in

Important identified risk	
	sections 2 and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures. ***Section 4.8:*** Timolol Eye disorders: choroidal detachment following filtration surgery
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Hypoglycaemia/diabetes**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of hypoglycaemia/diabetes is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycemia or to

Important identified risk	
	patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia. ***Section 4.8:*** Timolol Metabolism and nutrition disorders: hypoglycaemia
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Cardiac and vascular disorders**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of cardiac and vascular disorders is already included in *sections 4.3, 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.3:*** Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. ***Section 4.4:***

Important identified risk	
	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 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, beta-blockers should only be given with caution to patients with first degree heart block. 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. ***Section 4.8:*** Timolol Metabolism and nutrition disorders: hypoglycaemia
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Corneal toxicity – dry eye**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning dryness of eyes being induced in patients with corneal diseases is already included in *sections 4.4* and *4.8* of SmPC. It is also listed in *section 4* of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *Ophthalmic β-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.* ***Section 4.8:*** Bimatoprost/timolol *Eye disorders: eye dryness (common)*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Coadministration with adrenaline**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk

Important identified risk	
Routine risk minimisation measures	Warning on the increased risk when bimatoprost/timolol is coadministered with adrenaline is already included in *section 4.4* of SmPC. It is also listed in *section 2* of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Hypersensitivity to any allergen**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the increased risk of hypersensitivity is already included in *sections 4.3, 4.4* and *4.8* of SmPC. It is also listed in *sections 2* and *4* of PIL (risk communication to reduce the incidence of it) ***Section 4.3:*** *Hypersensitivity to the active substances or to any of the excipients.* ***Section 4.4:***

Important identified risk	
	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. ***Section 4.8:*** Timolol *Immune system disorders: Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important identified risk	
Safety concern	**Masking hyperthyroidism signs**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the risk of masking hyperthyroidism is already included in *section 4.4* of SmPC. It is also listed in *section 2* of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *Beta-blockers may also mask the signs of*

Important identified risk	
	hyperthyroidism.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important potential risk	
Safety concern	**Increase in intraocular pressure**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the risk of IOP increase is already included in *section 4.4* of SmPC. It is also listed in *section 2* of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *In studies of bimatoprost 0.3 mg/mL in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using [Invented name] with other prostaglandin analogs should be monitored for changes to their intraocular pressure.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be	Assessment of the effectiveness of risk minimisation measures on ongoing basis within

Important potential risk	
measure	continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important potential risk	
Safety concern	**Off-label use (cosmetic use for stimulation of eyelash growth)**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Bimatoprost/timolol should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events. Warning on this risk is already included in *section 4.1, 4.4* and *4.8* of SmPC. It is also listed in *sections 1, 2* and *4* of PIL (risk communication to reduce the incidence of it) ***Section 4.1:*** *Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.* ***Section 4.4:*** *Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and bimatoprost/timolol.* ***Section 4.8:*** Bimatoprost/timolol Eye disorders: growth of eyelashes (common)

Important potential risk	
	Bimatoprost Eye disorders: eyelash darkening
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Missing information	
Safety concern	**Use during pregnancy and lactation**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning regarding use of the product during pregnancy and lactation already included in *section 4.6* of SmPC. In addition is a listed in *section 2* of the PIL (risk communication to reduce the incidence of it) ***Section 4.6:*** <u>*Pregnancy*</u> *There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. [Invented name] should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.* *Bimatoprost* *No adequate clinical data in exposed pregnancies are available. Animal studies have*

Missing information	
	shown reproductive toxicity at high maternotoxic doses. *Timolol* *Epidemiological studies have not revealed malformative effects but 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 [Invented name] is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice.* *<u>Breastfeeding</u>* *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.* *Bimatoprost* *It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. [Invented name] should not be used by breast-feeding women.* *<u>Fertility</u>* *There are no data on the effects of bimatoprost/timolol on human fertility.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	None

Missing information	
(repeat as necessary)	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Missing information	
Safety concern	**Paediatric use**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on lack of established efficacy of product in paediatric patients already included in *section 4.2* of SmPC and in *section 2* of the PIL (risk communication to reduce the incidence of it) ***Section 4.2:*** *The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measure	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable

Missing information	
Impact of risk minimisation	Not applicable
Comment	Not applicable

V.2 RISK MINIMISATION MEASURE FAILURE

Not applicable.

V.3 SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Hyperpigmentation	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Macular oedema	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Respiratory disorders	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Choroidal detachment	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Hypoglycaemia/diabetes	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Cardiac and vascular disorders	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Corneal toxicity – dry eye	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None
Co-administration with adrenaline	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Hypersensitivity to any allergen	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Masking hyperthyroidism signs	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Increase in intraocular pressure	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Off-label use (cosmetic use for	SmPC sections 4.1, 4.4 and 4.8	None

stimulation of eyelash growth)	PIL sections 1, 2 and 4 Prescription only medicine	
Use during pregnancy and lactation	SmPC section 4.6 PIL section 2 Prescription only medicine	None
Paediatric use	SmPC section 4.2 PIL section 2 Prescription only medicine	None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

VI.1 ELEMENTS FOR SUMMARY TABLES IN THE EPAR

VI.1.1 SUMMARY TABLE OF SAFETY CONCERNS

Summary of safety concerns	
Important identified risks	• Hyperpigmentation • Macular oedema • Choroidal detachment • Hypoglycaemia/diabetes • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye • Co-administration with adrenaline • Hypersensitivity to any allergen • Masking hyperthyroidism signs
Important potential risks	• Increase in intraocular pressure • Off-label use (cosmetic use for stimulation of eyelash growth)
Missing information	• Use during pregnancy and lactation • Paediatric use

VI.1.2 TABLE OF ON-GOING AND PLANNED ADDITIONAL PHV STUDIES/ACTIVITIES IN THE PHARMACOVIGILANCE PLAN

Not applicable.

VI.1.3 TABLES OF POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

VI.1.4 SUMMARY OF RISK MINIMISATION MEASURES

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Hyperpigmentation	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Macular oedema	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Respiratory disorders	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4	None

	Prescription only medicine	
Choroidal detachment	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Hypoglycaemia/diabetes	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Cardiac and vascular disorders	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Corneal toxicity – dry eye	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None
Co-administration with adrenaline	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Hypersensitivity to any allergen	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Masking hyperthyroidism signs	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Increase in intraocular pressure	SmPC section 4.4 PIL section 2 Prescription only medicine	None
Off-label use (cosmetic use for stimulation of eyelash growth)	SmPC sections 4.1, 4.4 and 4.8 PIL sections 1, 2 and 4 Prescription only medicine	None
Use during pregnancy and lactation	SmPC section 4.6 PIL section 2 Prescription only medicine	None
Paediatric use	SmPC section 4.2 PIL section 2 Prescription only medicine	None

VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 OVERVIEW OF DISEASE EPIDEMIOLOGY

Ocular hypertension is 10-15 times more likely to occur than primary open-angle glaucoma, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will have pressures higher than 21 mm Hg, but only 1 of those people will have glaucoma. In approximately 3% of people with ocular hypertension, vision loss can result.

Between 3 and 6 million people are at risk for developing Primary Open Angle Glaucoma (POAG) due to elevated intraocular pressure (IOP).

Some studies have found that the average intraocular pressure in blacks is higher than in whites. In addition, average intraocular pressure in women (especially after menopause) is higher than in men.
Studies also show that men with ocular hypertension may be at a higher risk for glaucomatous damage.

Glaucoma is a group of eye diseases traditionally characterized by elevated intraocular pressure (IOP). **Open-angle glaucoma** is the most common type of glaucoma among populations of European or African descent, whereas angle-closure glaucoma is more common among populations of Asian descent. It is the second leading cause of blindness in the world (after cataracts) and the leading cause of blindness among African-Americans if left untreated.
Glaucoma affects one in 200 people aged 50 and younger, and one in 10 over the age of 80. The World Health Organization estimated that in 2010 glaucoma accounted for 2% of visual impairment and 8% of global blindness. If the condition is detected early enough, it is possible to arrest the development or slow the progression with medical and surgical means.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

[Bimatoprost/timolol] contains two different active substances (bimatoprost and timolol) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, a prostaglandin analogue. Timolol belongs to a group of medicines called beta-blockers. [Bimatoprost/timolol] is prescribed in adult patients with open-angle glaucoma or ocular hypertension when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.

The majority of patients with glaucoma or ocular hypertension eventually require adjunctive therapy to control their IOP. [Bimatoprost/timolol] combines two active substances in a single formulation for the reduction of IOP by the differential mechanisms of action and complementary pharmacology of the active ingredients. The fixed combination may lead to increased compliance since it is administered more conveniently than the individual products administered adjunctively.

Although the development of minor adverse effects, such as iris and eyelid hyperpigmentation, eyelash changes, conjunctival hyperemia, and iritis and macular edema (rarely occurred), which are common to prostaglandin's therapy (latanoprost, travoprost, tafluprost, bimatoprost, or isopropyl unoprostone), the efficiency and safety of bimatoprost have been extensively demonstrated.

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. Therefore, its use is not recommended in these patients.

In addition, bimatoprost/timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

VI.2.4 SUMMARY OF SAFETY CONCERNS

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language *(medical term)*	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Change in the colour of iris (the coloured part of the eye) *(Hyperpigmentation)*	Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iris pigmentation are not known.	You should advise with an ophthalmologist however these changes are solely cosmetic in nature, and have not posed a health risk in any form..
Blurred, reduced or abnormal vision *(Macular oedema)*	The macula is a very small area at the center of the retina - a thin layer of light-sensitive tissue that lines the back of the eye. Macular edema develops when blood vessels in the retina are leaking fluids. The macula does not function properly when it is swollen. Vision loss may be mild to severe, but in many cases, peripheral (side) vision remains.	Yes, by discontinuation of the treatment and consultation of an ophthalmologist.
Breathlessness or wheezing or increase of asthma symptoms *(Respiratory disorders)*	Respiratory disorders are adverse event related to systemic absorption of the drug. Bimatoprost/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.	Yes, by discontinuation of the treatment and immediate consultation of a doctor.
Problem in the surface layer of the eye after eye surgery *(Choroidal detachment)*	Choroidal detachment is the separation of the choroid from the sclera of the eye as a result of leakage of fluid from the vessels of the choroid. It occurs when pressure inside the eyeball is very low, usually after trauma or intraocular surgery.	Yes, by discontinuation of the treatment and immediate consultation of a doctor.

Very low level of blood sugar, diabetes *(Hypoglycaemia/diabetes)*	Beta-adrenergic receptor blocking agents may mask symptoms of hypoglycaemia such as tremors, tachycardia and blood pressure changes.	Yes, by informing your doctor in case of diabetes. If you experience any of the previously described symptoms talk to your doctor immediately.
Increased or decreased blood pressure, irregular, increased, or decreased heart rate (bradycardia) *(Cardiac and vascular disorders)*	Cardiac and vascular disorders are adverse event related to systemic absorption of the drug. These adverse events may occurred uncommonly (may affect up to 1 in 100 people). These effects should be considered in elderly and in patients with cardiac, respiratory or neurological diseas.e	Yes, by consultation of a doctor.
Irritation of the eye - dry eyes *(Corneal toxicity – dry eye)*	Signs and symptoms of eye irritation (e.g. burning, stinging, itching, tearing, redness), inflammation of the eyelid, inflammation in the cornea, blurred vision, decreased corneal sensitivity, dry eyes, corneal erosion (damage to the front layer of the eyeball), drooping of the upper eyelid (making the eye stay half closed) double vision, sensitivity to light, discharge from the eye, pain in the eye, have been reported.	Yes, by informing your ophthalmologist in case of appearance of such symptoms Your doctor should monitor you for local and systemic adverse effects.
Administration together with adrenaline *(Co-administration with adrenaline)*	In case of surgical anaesthesia, both the anesthesiologist and the ophthalmologist must be aware that eyedrops are readily absorbed through hyperemic incised conjunctivae. Although small in volume, these drops contain highly concentrated medication that can produce systemic results.	Yes, by informing the anaesthesiologist in case of timolol use
Allergic reaction *(Hypersensitivity to any allergen)*	Severe allergic reactions with swelling and difficulty breathing which could be life-threatening as well other allergic reactions (including rash, itching, hives) have bee reported.	Yes, by discontinuation of the treatment and immediate consultation of a doctor.
Overactivity of the thyroid gland	Use of timolol eye drops, because of it systemic absorption, may mask hyperthyroidism symptoms such heart	Yes, by informing your doctor if you have or overactivity of the thyroid

(Masking hyperthyroidism signs)	problems, brittle bones, thyrotoxic crisis, myasthenia gravis.	gland.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Increase in intraocular pressure	In studies of bimatoprost 0.3 mg/mL in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using [Invented name] with other prostaglandin analogs should be monitored for changes to their intraocular pressure.
Off-label use (cosmetic use for stimulation of eyelash growth)	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Patients must be advised that bimatoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension and should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events.

Missing information	
Risk	**What is known**
Use during pregnancy and lactation	There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. [bimatoprost/timolol] should not be used during pregnancy unless clearly necessary. Animal studies with bimatoprost have shown reproductive toxicity. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice. 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. It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. [Bimatoprost/timolol] should not be used by breast-feeding women.
Paediatric use	The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as

routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 PLANNED POST AUTHORISATION DEVELOPMENT PLAN

Not applicable.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Date	Safety concerns	Change
1.0	23.09.2016	**Important identified risks** • Hyperpigmentation • Macular oedema • Choroidal detachment • Hypoglycaemia/diabetes • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye • Co-administration with adrenaline • Hypersensitivity to any allergen • Masking hyperthyroidism signs **Important potential risks** • Increase in intraocular pressure • Off-label use (cosmetic use for stimulation of eyelash growth) **Missing information** • Use during pregnancy and lactation • Paediatric use	Initial version
1.0	04.11.2016	**NA**	Change of the description of the ATC code as per CZ comment during validation phase

PART VII: ANNEXES

Table of contents

ANNEX 1 – EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2 - SMPC & PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 0.3 mg/mL + 5 mg/mL eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colorless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including older people)
The recommended dose is one drop of [Invented name] in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing (see section 5.1).

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Renal and hepatic impairment

Bimatoprost/timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.

Method of administration

If more than one topical ophthalmic medicinal product is to be used, each one should be instilled at least 5 minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

[Invented name] eye drops solution is a sterile solution that does not contain a preservative.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

Patients should also be instructed that ocular solutions, if handled improperly, 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 solutions.

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 pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in [Invented name] 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, pulmonary and other adverse reactions as seen with systemic beta-blockers 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

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

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.

[Invented name] 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-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic β-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

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Hepatic

In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Ocular

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and bimatoprost/timolol. Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated.

After discontinuation of bimatoprost/timolol, pigmentation of iris may be permanent. After 12 months treatment with bimatoprost/timolol, the incidence of iris pigmentation was 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iridial pigmentation are not known. Iris color changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Macular oedema, including cystoid macular oedema, has been reported with bimatoprost/timolol. Therefore, [Invented name] should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

[Invented name] should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Skin

There is a potential for hair growth to occur in areas where bimatoprost/timolol solution comes repeatedly in contact with the skin surface. Thus, it is important to apply [Invented name] as instructed and avoid it running onto the cheek or other skin areas.

Other conditions

Bimatoprost/timolol has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

In studies of bimatoprost 0.3 mg/mL in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using [Invented name] with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with the bimatoprost/timolol fixed combination.

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, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

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.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. [Invented name] should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost

No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol

Epidemiological studies have not revealed malformative effects but 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 [Invented name] is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Breastfeeding

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.

Bimatoprost

It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. [Invented name] should not be used by breast-feeding women.

Fertility

There are no data on the effects of bimatoprost/timolol on human fertility.

4.7 Effects on ability to drive and use machines

[Invented name] has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Bimatoprost/timolol

Summary of the safety profile

The adverse reactions reported in clinical studies using bimatoprost/timolol were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for bimatoprost/timolol have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using bimatoprost/timolol were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26% of patients and led to discontinuation in 1.5% of patients.

Tabulated list of adverse reactions

The following adverse reactions have been reported with bimatoprost/timolol (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness).

The frequency of possible adverse reactions listed below is defined using the following convention:

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	Frequency cannot be estimated from available data

System Organ Class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	headache, dizziness
Eye disorders	Very common	conjunctival hyperaemia
	Common	superficial punctuate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity

		worsened, blepharitis, eyelid oedema, eye irritation, epiphora, growth of eyelashes
	Uncommon	iritis, conjunctival oedema, eyelid pain, asthenopia, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus, eyelid retraction
	Not known	cystoid macular oedema
Respiratory, thoracic and mediastinal disorders	Common	rhinitis
	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Skin and subcutaneous tissue disorders	Common	blepharal pigmentation, hirsutism, periocular skin hyperpigmentation

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with [Invented name] are listed below:

Bimatoprost

System Organ Class	**Adverse reaction**
Eye disorders	allergic conjunctivitis, eyelash darkening, blepharospasm, retinal haemorrhage, uveitis, periorbital erythema, blurred vision.
Vascular disorders	hypertension
General disorders and administration site condition	asthenia
Gastrointestinal disorders	nausea

Investigations	liver function tests (LFT) abnormal

Timolol

Like other topically applied ophthalmic drugs, [Invented name] (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. 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 [Invented name] are listed below:

System Organ Class	**Adverse reaction**
Immune system disorders	Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Insomnia, depression, nightmares, memory loss
Nervous system disorders	Syncope, cerebrovascular accident, increase in signs and symptoms of myasthenia gravis, paraesthesia, cerebral ischaemia
Eye disorders	Decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery (see section 4.4), keratitis, blurred vision
Cardiac disorder	Atrioventricular block, cardiac arrest, arrhythmia, bradycardia, cardiac failure, congestive heart failure, chest pain, palpitations, oedema
Vascular disorders	Hypotension, Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic and mediastinal disorders	Cough.
Gastrointestinal disorders	Dysgeusia, nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash

Musculoskeletal and connective tissue disorders	Myalgia
Reproductive system and breast disorders	Sexual dysfunction, decreased libido
General disorders and administration site conditions	Asthenia/fatigue

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A topical overdose with [Invented name] is not likely to occur or to be associated with toxicity.

Bimatoprost

If [Invented name] is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70-times higher than the accidental dose of one bottle of [Invented name] in a 10 kg child.

Timolol

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

If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents – ATC code: S01ED51

Mechanism of action

[Invented name] consists of two active substances: bimatoprost and timolol. 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.

Bimatoprost/timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F2_{\alpha}$ ($PGF2_{\alpha}$) that does not act through any known prostaglandin receptors.

Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects

The IOP-lowering effect of bimatoprost/timolol is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

Bimatoprost/timolol medicinal product

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost/timolol treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies where systemic absorption was measured, no accumulation was observed with either of the individual components.

Bimatoprost

Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean C_{max} and AUC $_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 1/hr/kg.

Characteristics in older people

After twice daily dosing, the mean AUC $_{0\text{-}24hrs}$ value of 0.0634 ng•hr/mL bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/mL in young healthy adults.

However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

Timolol

After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/mL in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

5.3 Preclinical safety data

Bimatoprost/timolol medicinal product

Repeated dose ocular toxicity studies on bimatoprost/timolol showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium hydrogen phosphate heptahydrate
Citric acid monohydrate
Sodium hydroxide or/and Hydrochloric Acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months
4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque 5 mL LDPE bottle and white Novelia nozzle (HDPE and silicone) with a blue tip and sealed with a white HDPE cap.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

[Invented name] 0.3 mg/mL + 5 mg/mL eye drops, solution
bimatoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [Invented name] is and what it is used for

[Invented name] contains two different active substances (bimatoprost and timolol) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, a prostaglandin analogue. Timolol belongs to a group of medicines called beta-blockers.

Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up and could eventually damage your sight (an illness called glaucoma). [Invented name] works by reducing the production of liquid and also increasing the amount of liquid that is drained. This reduces the pressure inside the eye.

[Invented name] eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This high pressure can lead to glaucoma. Your doctor will prescribe you [Invented name] when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.
[Invented name] eye drops solution is a sterile solution that does not contain a preservative.

2. What you need to know before you use [Invented name]

Do not use [Invented name]

- if you are allergic to bimatoprost, timolol, beta-blockers or any of the other ingredients of this medicine (listed in section 6)
- if you have now or have had in past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough)
- if you have heart problems such as low heart rate, heart block, or heart failure

Warnings and precautions

Talk to your doctor before using [Invented name] if you have now or have had in the past:

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure,
- disturbances of heart rate such as slow heart beat
- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- diabetes as timolol may mask signs and symptoms of low blood sugar
- severe allergic reactions
- liver or kidney problems
- eye surface problems
- separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye
- known risk factors for macular oedema (swelling of the retina within the eye leading to worsening vision), for example, cataract surgery

Tell your doctor before surgical anaesthesia that you are using [Invented name] as timolol may change effects of some medicines used during anaesthesia.

[Invented name] may cause your eyelashes to darken and grow, and cause the skin around the eyelid to darken too. The colour of your iris may also go darker over time. These changes may be permanent.

The change may be more noticeable if you are only treating one eye.

Children and adolescents

[Invented name] should not be used in children and teenagers under 18.

Other medicines and [Invented name]

[Invented name] can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are using or intend to use:

- medicines to lower blood pressure
- heart medicine
- medicines to treat diabetes
- quinidine (used to treat heart conditions and some types of malaria)
- medicines to treat depression known as fluoxetine and paroxetine

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use [Invented name] if you are pregnant unless your doctor still recommends it.

Do not use [Invented name] if you are breast-feeding. Timolol may get into your breast milk.

Ask your doctor for advice before taking any medicine during breast-feeding.

Driving and using machines

[Invented name] may cause blurred vision in some patients. Do not drive or use machines until the

symptoms have cleared.

3. How to use [Invented name]

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one drop once a day, either in the morning or in the evening in each eye that needs treatment. Use at the same time each day.

Do not allow the tip of the multi dose container to touch the eye or areas around the eye. It could cause injury to your eye. The eye drops solution may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision.

To avoid possible contamination of the multi-dose container, keep the tip of the multi-dose container away from contact with any surface.

Instructions for use

Before instillation of the eye drops:

- Wash your hands before opening the bottle.
- Do not use this medicine if you notice that the tamper-proof seal on the bottle neck is broken before you first use it.
- When using for the first time, before delivering a drop to the eye, you should first of all practise using the dropper bottle by squeezing it slowly to deliver one drop into the air, away from the eye.
- When you are confident that you can deliver one drop at a time, choose the position that you find most comfortable for the instillation of the drops (you can sit down, lie on your back, or stand in front of a mirror).

Instillation:

1. Hold the bottle directly below the cap and turn the cap to open the bottle. Do not touch anything with the tip of the bottle to avoid contamination of the solution.

2. Tilt your head backwards and hold the bottle above your eye.

3. Pull the lower eyelid down and look up. Squeeze the bottle gently in the middle and let a drop fall into your eye. Please note that there might be a few seconds delay between squeezing and the drop coming out. Do not squeeze too hard.

If a drop misses your eye, try again.

If you are not sure how to administer your medicine, ask your doctor, pharmacist or nurse.

4. Blink a few times so that the drop spreads over the eye.

5. Repeat the instructions 2. – 4. to deliver a drop into the other eye also, if your doctor has instructed you to do this. Sometimes only one eye needs to be treated and your doctor will advise if this applies to you and which eye needs treatment.

6. After use and prior to recapping, the bottle should be shaken once in a downwards direction, without touching the dropper tip, in order to remove any residual liquid on the tip. This is necessary in order to ensure delivery of subsequent drops.

7. After you have used all doses there will be some [Invented name] left in the bottle. You should not be concerned since an extra amount of [Invented name] has been added and you will get the full amount of [Invented name] that your doctor has prescribed. Do not attempt to use the excess medicine remaining in the bottle after you have completed the course of treatment.

Do not use the eye drops for longer than 28 days after first opening the bottle.

If you use [Invented name] with another eye medicine, leave at least 5 minutes between putting in [Invented name] and the other medicine. Use any eye ointment or eye gel last.

If you use more [Invented name] than you should

If you use more [Invented name] than you should, it is unlikely to cause you any serious harm. Put your next dose in at the usual time. If you are worried, talk to your doctor or pharmacist.

If you forget to use [Invented name]

If you forget to use [Invented name], use a single drop as soon as you remember, and then go back to your regular routine. Do not use a double dose to make up for a forgotten dose.

If you stop using [Invented name]

[Invented name] should be used every day to work properly.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist. Do not stop using [Invented name] without speaking to your doctor.

The following eye side effects may be seen with bimatoprost/timolol:

Very common (may affect more than 1 in 10 people):
- eye redness

Common (may affect up to 1 in 10 people):
- burning, itching, stinging
- sensitivity to light
- eye pain
- sticky eyes
- dry eyes
- a feeling of something in the eye
- small breaks in the surface of the eye with or without inflammation
- difficulty in seeing clearly
- redness and itching of the eyelids
- darkening of the eyelids, darker skin colour around the eyes
- headache
- longer eyelashes
- eye irritation
- watery eyes
- swollen eyelids
- reduced vision
- runny nose
- hair growing around the eye
- dizziness

Uncommon (may affect up to 1 in 100 people):
- iris inflammation
- swollen conjunctiva (see-through layer of the eye)
- painful eyelids
- tired eyes
- in-growing eyelashes
- darker iris colour
- eyes appear sunken
- eyelid has moved away from the surface of the eye
- shortness of breath

Not known (frequency cannot be estimated from available data):

- cystoid macular oedema (swelling of the retina within the eye leading to worsening vision)
- difficulty breathing / wheezing

Additional side effects have been seen in patients using eye drops containing bimatoprost and so may possibly be seen with [Invented name]:

- allergic reaction in the eye, darkening of the eyelashes, darkening of the iris colour, increased blinking, bleeding in the back of the eye (retinal bleeding), inflammation within the eye
- high blood pressure
- weakness
- an increase in blood test results that show how your liver is working

Additional side effects have been seen in patients using eye drops containing timolol and so may possibly be seen with [Invented name].

Like other medicines applied into eyes, timolol is absorbed into the blood. This may cause similar side effects as seen with "intravenous" and /or "oral" beta-blocking agents. The chance of having side effects after using eye drops is lower than when medicines are for example, taken by mouth or injected. Listed side effects include reactions seen within the class of beta-blockers when used for treating eye conditions:

- severe allergic reactions with swelling and difficulty breathing which could be life-threatening; allergic reactions (including rash, itching, hives);
- low blood sugar
- difficulty sleeping, nightmares, depression; memory loss
- fainting; stroke; decreased blood flow to the brain; worsening of myasthenia gravis (increased muscle weakness); tingling sensation; dizziness
- decreased sensation of your eye surface; double vision; drooping eyelid; separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye; inflammation of the surface of the eye; blurred vision
- heart failure; irregularity or stopping of the heartbeat; slowing of heart rate; slow or fast heartbeat; too much fluid, mainly water, accumulating in the body; chest pain
- low blood pressure; swelling or coldness of your hands, feet and extremities, caused by constriction of your blood vessels
- cough
- diarrhoea; stomach pain; feeling and being sick; changes in your taste sensation; indigestion; dry mouth
- red scaly patches on skin; skin rash; hair loss
- muscle pain
- reduced sexual urge; sexual dysfunction
- tiredness

Other side effects reported with eye drops containing phosphates

In very rare cases, some patients with severe damage to the clear layer at the front of the eye (the cornea) have developed cloudy patches on the cornea due to calcium build-up during treatment.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system <to be completed nationally>. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Invented name]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.

After first opening, the product may be stored for a maximum of 28 days. No special storage conditions are required.

Do not use this medicine if you notice that the seal is broken the first time you use the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Invented name] contains
- The active substances are bimatoprost 0.3 mg/mL and timolol 5 mg/mL corresponding to timolol maleate 6.83 mg/mL.

- The other ingredients are sodium chloride, disodium hydrogen phosphate heptahydrate, citric acid monohydrate, sodium hydroxide or/and hydrochloric acid (for pH adjustment) and water for injections.

What [Invented name] looks like and contents of the pack
[Invented name] is a presented as a clear, colorless aqueous solution filled in a white opaque 5 ml LDPE bottle and white Novelia nozzle (HDPE and silicone) with a blue tip and sealed with a white HDPE cap and packed in cardboard box.

The following pack sizes are available: cartons containing 1 or 3 bottles

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

This leaflet was last revised in

ANNEX 3 - WORLDWIDE MARKETING AUTHORISATION BY COUNTRY (INCLUDING EEA)

A3.1 LICENSING STATUS IN THE EEA

Not applicable.

A3.2 LICENSING STATUS IN THE REST OF THE WORLD

Not applicable.

ANNEX 4 - SYNOPSIS OF ON-GOING AND COMPLETED CLINICAL TRIAL PROGRAMME

Not applicable.

ANNEX 5 - SYNOPSIS OF ON-GOING AND COMPLETED PHARMACOEPIDEMIOLOGICAL STUDY PROGRAMME

Not applicable.

ANNEX 6 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN CATEGORIES 1-3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN RMP PART III

Not applicable.

ANNEX 7 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Not applicable.

ANNEX 8 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 9 - NEWLY AVAILABLE STUDY REPORTS FOR RMP PARTS III & IV

Not applicable.

ANNEX 10 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable.

ANNEX 11 - MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable.

ANNEX 12 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

'[Bimatoprost/timolol] 0.3 mg/ml + 5 mg/ml, preservative-free eye drops, solution'- SmPC

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Module 2.4 - Non-clinical Overview

Module 2.5 – Clinical Overview

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Abbreviations:

PG	:	Prostaglandins
PG (FP)	:	Prostaglandin F recepror
IOP	:	Intraocular pressure
OAG	:	Open –angle glaucoma
OH	:	Ocular hypertension
POAG	:	Primary open-angle glaucoma