[TRAVOPROST + TIMOLOL] 40 MCG/ML + 5 MG/ML, PRESERVATIVE-FREE EYE DROPS, SOLUTION

RISK MANAGEMENT PLAN

TRAVO-TIMOL PF-v1-260916

TABLE OF CONTENTS

Active substance(s) (INN or common name):	**Travoprost** **Timolol (as timolol maleate)**
Pharmaco-therapeutic group (ATC Code):	**S01ED51**
Name of Marketing Authorisation Holder or Applicant:	**Pharmathen SA**
Number of medicinal products to which this RMP refers:	**2**
Product(s) concerned (brand name (s)): **DK/H/2707/001/DC** (DK, IT, AT, DE) **DK/H/2714/001/DC** (DK, EL, CY)	 **Travoprost / Timolol Pharmathen** (DK, IT, AT, DE) **GALYA** (DK, EL, CY)

Active substance(s) (INN or common name):	**Travoprost** **Timolol (as timolol maleate)**
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/2708/001/DC** (DK, FR, BE, NL, LU, ES)	 **Travoprost/Timolol Horus Pharma** (DK, FR, BE, NL, LU, ES)

Active substance(s) (INN or common name):	**Travoprost** **Timolol (as timolol maleate)**
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	**1**

this RMP refers:	
Product(s) concerned (brand name (s)): **DK/H/2713/001/DC** (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, HU, EL, PT)	 **Vizitrav Duo** (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, HU, EL, PT)

Data lock point for this RMP	20.09.2016	Version number	TRAVO-TIMOL PF-v1-260916
Date of final sign off	26.09.2016		

RISK MANAGEMENT PLAN

Part I: Product(S) OVERVIEW

[Travoprost+ Timolol] 40µg/mL + 5mg/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 Summary of RMP		-	Not applicable
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 125 of this document	Not applicable

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

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

Deputy QPPV name	(MD, PhD)
Deputy QPPV signature	
Contact person for this RMP	
E-mail address or telephone number of contact person	

Overview of versions:

Version number of last agreed RMP:	-
Version number	TRAVO-TIMOL PF-v1-260916
Agreed with	DK/H/2707/001/DC DK/H/2714/001/DC DK/H/2708/001/DC DK/H/2713/001/DC

Current RMP versions under evaluation:

Not applicable.

Invented name (s) in the European Economic Area (EEA)	**Travoprost / Timolol Pharmathen 40µg/mL + 5mg/mL, eye drops, solution** (DK, IT, AT, DE) **GALYA 40µg/mL + 5mg/mL, eye drops, solution** (DK, EL, CY) **Travoprost/Timolol Horus Pharma 40µg/mL + 5mg/mL, eye drops, solution** (DK, FR, BE, NL, LU, ES) **Vizitrav Duo 40µg/mL + 5mg/mL, eye drops, solution** (DK, FR, BE, NL, LU, DE, ES, PL, SK, RO, BG, LT, EE, HU, EL, PT)
Authorisation procedure	**DK/H/2707/001/DC** **DK/H/2714/001/DC** **DK/H/2708/001/DC** **DK/H/2713/001/DC**
Brief description of the product including:	
• Chemical class	Travoprost is a prostaglandin $F_{2\alpha}$ analogue althought timolol is a non-selective adrenergic blocking agent. Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, ATC code: S01ED51.
• Summary of mode of action	[Invented name] contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost, a prostaglandin $F_{2\alpha}$ analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose. Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant

	action is related to reduced aqueous humour formation and a slight increase in outflow facility. <u>Secondary pharmacology</u> Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily).
• Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Not applicable.
Indication (s) in the EEA Current (if applicable)	Not applicable.
Proposed (if applicable)	[Invented name] is indicated in adults for the decrease of intraocular pressure (IOP) in 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)	<u>Posology</u> *Use in adults, including the older population* The dose is one drop of [Invented name] in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day. If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. <u>Special Populations</u> *Hepatic and renal impairment* No studies have been conducted with travoprost/timolol or

	with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dose adjustment was necessary in these patients. Patients with hepatic or renal impairment are unlikely to require dose adjustment with [Invented name]. *Paediatric population* The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have not been established. No data are available. <u>Method of administration</u> For ocular use. The patient should remove the protective overwrap immediately prior to initial use. [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. 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. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart.

	When substituting another ophthalmic antiglaucoma medicinal product with [Invented name], the other medicinal product should be discontinued and [Invented name] should be started the following day. Patients must be instructed to remove soft contact lenses prior to application of [Invented name] and wait 15 minutes after instillation of the dose before reinsertion.
Pharmaceutical form (s) and strengths Current (if applicable)	Not applicable.
Proposed (if applicable)	Eye drops, solution (eye drops). Clear, colorless aqueous solution Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as 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

'[Travoprost+ Timolol] 40µg/mL + 5µg/mL, preservative free eye drops, solution' is a generic formulation of *DuoTrav 40µg/mL + 5 mg/mL eye drops, solution (Alcon Laboratories)'.* 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: *[Travoprost+ Timolol] 40µg/mL + 5µg/mL, preservative free eye drops, solution'* is indicated in adults for the decrease of intraocular pressure (IOP) in 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):

- **Travoprost / Timolol Pharmathen 40µg/mL + 5mg/mL, eye drops, solution**
- **GALYA 40µg/mL + 5mg/mL, eye drops, solution**
- **Travoprost/Timolol Horus Pharma 40µg/mL + 5mg/mL, eye drops, solution**
- **Vizitrav Duo 40µg/mL + 5mg/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 ***Travoprost/Timolol Combination*** A one-day ocular irritation and comfort study with Travoprost/Timolol Ophthalmic Solution (0.004% / 0.5% w/v) in rabbits, dosed two drops to the right eye every 30 minutes for 10 doses, has revealed only moderate conjunctival congestion and minimal discomfort, comparable with the individual active components. Systemic single dose studies were not conducted with the combined drugs. A 7.5 mL bottle of DuoTrav (40 µg/mL travoprost with 5 mg/mL timolol) contains 0.3 mg travoprost and 37.5 mg timolol. Exposure to the entire contents of a container by a 10 kg child would result in exposure of 0.03 mg/kg travoprost and 3.75 mg/kg timolol. The poor oral bioavailability of travoprost mitigates the hazard of accidental ingestion. Timolol is orally bioavailable, but has a low order of toxicity (mouse/rat oral LD50 ~ 1000 mg/kg). ***Travoprost*** Travoprost was demonstrated to have a low order of acute toxicity. No LD50 of travoprost has been established. No mortalities occurred in rats administered travoprost intravenously at a dose of 10 mg/kg (250,000-times the proposed clinical exposure) or in mice given up to 100 mg/kg/day (2,500,000-times the proposed clinical exposure). The most frequent clinical observations were discoloured urine and red material around the nose in rats, and lethargy and diarrhea in mice. Administration of travoprost ophthalmic solution, up to 0.01%, two drops every half-hour for five or six hours, did not result any significant ocular or systemic effects. ***Timolol*** Acute oral dosing studies established an LD50 of approximately 1000 mg/kg for mice and rats. The most frequent clinical observations were decreased activity and bradypnea. Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by	Unrelated

<table>
<tr><th>Safety from non- clinical studies</th><th>Relevance to human usage</th></tr>
<tr><td>Toxicity</td><td></td></tr>
<tr><td>bishydroxycoumarin in the dog.</td><td></td></tr>
<tr><td>Repeated dose toxicity

Travoprost/Timolol Combination
Studies conducted to evaluate the potential ocular and systemic effects of the Travoprost/Timolol Solution consisted of two repeated-dose topical ocular studies, a 3-month rabbit study (with a 6-week interim analysis) and a 9-month rabbit study.

Repeated Dose Toxicity Studies with Travoprost/Timolol Ophthalmic Solution

<table>
<tr><th>Animal species, family</th><th>Number of animals/ groups</th><th>Concentration (%)</th><th>Dosing method</th><th>Dosing period</th><th>Results</th></tr>
<tr><td>Rabbit, pigmented</td><td>8/sex (3/sex were euthanized at 6 weeks)</td><td>Vehicle-control
Travoprost 0.004%/Timolol 0.5%
Travoprost 0.02%/Timolol 0.5%
Travoprost 0.02%</td><td>One drop in the right eye, 3 times daily</td><td>3 months (interim analysis at 6 weeks)</td><td>No significant ocular or systemic toxicity</td></tr>
<tr><td>Rabbit, pigmented</td><td>6/sex</td><td>Vehicle-control
Travoprost 0.004%/Timolol 0.5%
Travoprost 0.02%/Timolol 0.5%
Travoprost 0.02%
Timolol 0.5%</td><td>One drop in the right eye, 3 times daily</td><td>9 months</td><td>No significant ocular or systemic toxicity</td></tr>
</table>
The nonclinical dosing regimen was 3-times and 15-times the clinical dose for timolol and travoprost, respectively.

In both studies, thorough ocular evaluations, consisting of biomicroscopic slit lamp examinations, indirect ophthalmic examinations, corneal pachymetry, intraocular pressure (IOP) measurements and specular microscopy of the corneal endothelium (9-month study only), revealed no significant ocular effects even with chronic administration at these doses. Systemic evaluations, including physical examinations, body weight</td><td>Unrelated</td></tr>
</table>

Safety from non- clinical studies	Relevance to human usage
Toxicity	
measurements and clinical pathology evaluations, gross and microscopic pathology, likewise demonstrated no significant toxicity. Maximum mean plasma travoprost free-acid and timolol concentrations at the end of 9 months treatment were 0.509 ± 0.231 ng/mL travoprost and 6.06 ± 0.68 ng/mL timolol, for the 0.02% travoprost/0.5% timolol group. These concentrations were similar to groups receiving the single entities. The results showed that the systemic exposure to both drugs which was not significantly altered by the concomitant administration. The mean plasma levels of travoprost free-acid in these rabbit studies were substantially higher than those measured in clinical subjects for either drug, demonstrating good exposure-based safety margins. No chronic studies of greater than 9 months duration were conducted with Travoprost/Timolol fixed Combination. ***Travoprost*** Topical ocular administration of travoprost ophthalmic solution, 0.01%, three times a day for six months, in rabbits, resulted in no significant ocular or systemic effects. Iris pigmentation and a species specific increase in palpebral fissure and increase in lid retraction was observed in some monkeys receiving 0.0015%, 0.004% or 0.012% travoprost ophthalmic solution for up to one year. No other significant ocular or systemic effects were seen. The increased iridial pigmentation observed in monkeys and also in humans during chronic ocular treatment with travoprost is considered to be a class effect of prostaglandins. It is of particular interest that naturally occurring prostaglandins such as PGF2" and PGE2 also cause increased pigmentation of the iris in cynomolgus monkeys. It should also be noted that both cynomolgus monkey and human iridial melanocytes express FP receptors in their cell membrane, and since travoprost is a selective FP receptor agonist, it implies that the effect is mediated by FP receptors in the melanocytes. Subchronic intravenous administration of travoprost in rats at all doses employed (100 to 1000 micrograms/kg/day) resulted in trace-to-moderate hyperostosis and bone fibrosis. Incidence and severity were dose related, and determined bone to be a target organ of toxicity in rats. Similar studies in mice resulted in no significant systemic effects at doses of up to 1000 Fg/kg/day. Chronic systemic administration (subcutaneous) of travoprost to	

Safety from non- clinical studies	Relevance to human usage
Toxicity	
rats at doses of 30 and 100 micrograms/kg/day resulted in dose-related hyperostosis and bone fibrosis similar to that observed in the subchronic study. No effect was observed in bone at 10 micrograms/kg/day (250-times the proposed clinical exposure), which was considered the no effect level. ***Timolol*** No adverse ocular effects were observed in rabbits and dogs administered Timolol Maleate Ophthalmic Solution topically in studies lasting one and two years, respectively. Timolol was administered orally to rats at dose levels 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident. In a 54 week oral study, timolol was administered to dogs at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day. In rats treated with 100 to 400 mg/kg timolol maleate for seven weeks, excessive salivation seen 5 to 10 minutes after dosing has a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptyalism, muscle tremors and transient pale extremities. In dogs, doses of 200 mg/kg timolol maleate or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15 day intravenous toxicity study.	
Carcinogenicity Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day travoprost, did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the	Unrelated

Safety from non- clinical studies	Relevance to human usage
Toxicity	
mouse study. The high dose (100 mcg/kg/day) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD), based on plasma active drug levels. In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the MRHOD). This was not observed in rats administered oral doses equivalent to approximately 14,000 times the MRHOD. In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps, and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the MRHOD). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus 48 and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, 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. No carcinogenicity studies were conducted with Travoprost/Timolol fixed Combination Solution.	
Mutagenesis Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes. Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay	Unrelated

Safety from non- clinical studies	Relevance to human usage
Toxicity	
(doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests, the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA 100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. No mutagenicity studies were conducted with Travoprost/Timolol fixed Combination Solution.	
Reproduction & Teratology Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day [250 times the MRHOD of 0.04 µg/kg/day]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD). Travoprost was teratogenic in rats, at an intravenous (IV) dose of 10 µg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1.0 :g/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD). In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of =0.12 µg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity. Reproduction and fertility studies with timolol maleate in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the MRHOD. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the MRHOD	There are no or limited amount of data from the use of travoprost/timolol or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary

Safety from non- clinical studies	Relevance to human usage
Toxicity	
demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the MRHOD, in this case without apparent maternotoxicity. No reproduction or teratology studies were conducted with Travoprost/Timolol fixed Combination Solution.	

Safety from non-clinical studies	Relevance to human usage
General safety pharmacology	
According to the EMA Scientific Discussion on Duotrav, the clinical development to assess the safety of travoprost/timolol eye drops consisted of 6 studies and included a total of 1496 participants. Seven hundred twenty one patients have been exposed to travoprost 0.004%/timolol 0.5%, 200 patients to latanoprost 0.005%/timolol 0.5%, 313 patients to concomitant administration of Travatan +timolol 0.5%, 101 patients to Travatan as monotherapy, and 190 patients exposed to timolol 0.5% as monotherapy. The overall incidence of AEs in travoprost/timolol treatment group across individual studies ranged from 49.1% to 69.6% and did not significantly differ to that seen in the comparator groups, i.e. Travatan plus timolol treatment group (from 48.4 to 68.4%), latanoprost/timolol (45.5%), Travatan (52.3%) and timolol (from 48.8 to 53.3%). The most commonly reported ocular AEs (hyperemia, ocular discomfort and eye pruritus) were considered related to the study drug and were generally well tolerated and did not lead to a higher incidence of treatment discontinuation with the exception of hyperemia (1.9% in travoprost/timolol vs 0.0% in Latanoprost/timolol). Other treatment-related AEs that occurred with exposure to travoprost/timolol included hair disorder (changes in eyelash), blurred vision, ocular pain, photophobia and keratitis. An analysis of changes in cardiovascular parameters (pulse rate, systolic blood pressure and diastolic blood pressure) has been performed, the results of which are reassuring with no new or	Safety and efficacy profile of travoprost/timolol fixed combination solution in human is well established

unexpected safety concerns. The CHMP concluded that the benefit of the concomitant administration of travoprost plus timolol was demonstrated at the time of the granting the marketing authorisation for Travatan. Therefore, the efficacy as well as the safety and tolerance of the fixed dose combination of travoprost/timolol eye drops solution is considered to be adequately demonstrated (Duotrav EMA Scientific Discussion).	
Mechanisms for drug interactions	
No specific interaction studies have been performed with travoprost/timolol combination *Beta-adrenergic blocking agents:* Patients who are receiving a beta-adrenergic blocking agent orally and travoprost/timolol combination should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. *Calcium antagonists:* Caution should be used in the coadministration of beta-adrenergic blocking agents, such as the timolol found in DuoTrav, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided. *Catecholamine-depleting drugs:* Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension. *Digitalis and calcium antagonists:* The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. *Quinidine:* Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6. *Clonidine:* Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of	Unrelated

clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate. *CNS Depressants:* Although specific drug interaction studies have not been conducted with DuoTrav, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. *Tricyclic Antidepressants:* Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with DuoTrav can lead to interference in IOP lowering effect. No data are available on the level of circulating catecholamines after DuoTrav is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. *Epinephrine:* Mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.	
References of module SII	*'[Travoprost+ Timolol] 40µg/mL + 5µg/mL, eye drops, solution'* - SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution.* - SmPC DuoTrav™ – product Monograph. Alcon Canada Inc. Revised March 2008 FDA Travatan label 2011 EMA – DuoTrav Scientific discussion Module 2.5-Clinical overview

SII Conclusions on non-clinical data

Safety and efficacy profile of travoprost/timolol combination in humans is well established.

In monkeys, administration of travoprost/timolol twice–daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids.

Travoprost
Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity.
Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered 3H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).

Timolol
Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).

The most commonly reported treatment-related AEs that occurred with exposure to travoprost/timolol included hair disorder (changes in eyelash), blurred vision, ocular pain, photophobia and keratitis.
An analysis of changes in cardiovascular parameters (pulse rate, systolic blood pressure and diastolic blood pressure) has been performed, the results of which are reassuring with no new or unexpected safety concerns.

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

Module SIII: Clinical trial exposure

SIII.1 Brief overview of development

'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution' is a generic formulation of *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution (Alcon Laboratories).* This is being a 'hybrid' application under the Article 10(3) of European Directive 2001/83/EC.

SIII.2 Clinical Trial exposure

No changes as new indication, route of administration of new target population have been occurred following Marketing Authorization license for *''[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution'* product.

Based on the SmPC of the product as well as in the scientific discussion of the EMA outcome from clinical trial in special populations are summarized in the table below:

Special population	
Clinical studies in special populations	No studies in special populations have been performed.

Five clinical studies were conducted for DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution (Alcon Laboratories) to support the efficacy and safety of the fixed dose combination of travoprost/timolol in the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. These studies were multicenter, randomised, double-masked, parallel group, controlled clinical safety and efficacy trials.

Summary of Safety/Efficacy Trials of Travoprost/Timolol Eye Drops

Study # (Study Type / Location)	**Study Design**	**Treatment Duration**	**Patient Population**	**Treatment Groups**	**Dosing[a]**	**No. of Sites[b]**	**No. Patients Randomized (ratio)**	**Status**
C-02-03 Safety/Efficacy Posology Europe	Randomized, double-masked, parallel group	6 weeks	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • Travoprost/Timolol	• 1 drop AM • 1 drop PM	14	92 (1:1)	Completed
C-01-69 Safety/Efficacy Contribution of Elements US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN • Timolol	• 1 drop AM • 1 drop PM • 1 drop BID	33	263 (1:1:1)	Completed
C-01-70 Safety/Efficacy Concomitant administration #1 US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN+Timolol	• 1 drop AM • 1 drop PM + 1 drop AM	19	316 (1:1)	Completed
C-02-41 Safety/Efficacy Concomitant administration #2 US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN+Timolol • Timolol	• 1 drop AM • 1 drop PM + 1 drop AM • 1 drop BID	26	403 (2:2:1)	Completed
C-02-28 Safety/Efficacy Comparative Europe, Australia, New Zealand, Asia	Randomized, double-masked, parallel group	12 months	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • Latanoprost/Timolol (XALACOM)	• 1 drop AM • 1 drop AM	41	408 (1:1)	Completed

Travoprost/Timolol = Travoprost 40 µg/ml/Timolol 5 mg/ml Eye Drops, Solution
TRAVATAN = Travoprost 40 µg/ml Eye Drops, Solution
Timolol = Timolol 5 mg/ml Eye Drops, Solution
Latanoprost/Timolol (XALACOM) = Latanoprost 50 µg/ml/Timolol 5 mg/ml Eye Drops, Solution
Latanoprost = Latanoprost 50 µg/ml Eye Drops, Solution
[a] In each study eye
[b] Number of sites that enrolled patients

The objective of these studies is described in the table below:

Study number	**Objective**
C-02-03	To compare travoprost/timolol Eye Drops dosed in the morning to travoprost/timolol Eye Drops dosed in the evening
C-01-69	To compare the safety and efficacy of travoprost/timolol Eye Drops dosed once-daily in the morning to Travatan dosed once-daily in the evening and timolol 5 mg/ml Eye Drops dosed twice daily in a contribution-of-elements design
C-01-70 and C-02-41	To compare travoprost/timolol Eye Drops dosed once-daily in the morning to the concomitant administration of Travatan dosed once-daily in the evening plus timolol 5 mg/ml Eye Drops dosed once-daily in the morning
C-02-28	To compare travoprost/timolol Eye Drops to Latanoprost 50 µg/ml/timolol 5 mg/ml Eye Drops, Solution, both dosed once-daily in the morning

Travoprost/timolol Eye Drops administered once-daily is safe and well-tolerated in patients with open- angle glaucoma or ocular hypertension based upon an overall review of adverse events which includes an assessment of seriousness (serious/non-serious), treatment relatedness, most common events and rate of discontinuation due to adverse events.
A similar safety profile was observed comparing therapy with the combination product (travoprost/timolol Eye Drops) to concomitant therapy with the individual components (Travatan + timolol 5 mg/ml) or monotherapy with each component (Travatan; timolol 5 mg/ml).
No clinically relevant differences were observed when comparing the safety profiles of travoprost/timolol Eye Drops and latanoprost/timolol Eye Drops in patients with open angle glaucoma or ocular hypertension having up to 12 months of exposure to study drug.
Overall travoprost/timolol Eye Drops administered once-daily is safe and well-tolerated in patients with open-angle glaucoma or ocular hypertension based the assessment of adverse events (DuoTrav Scientific discussion-EMEA).

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 Travoprost/timolol should be either used with caution or it is not recommended.

Special Population	
Renal and Hepatic Impairment	No studies have been conducted with travoprost/timolol or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dose adjustment was necessary in these patients. Patients with hepatic or renal impairment are unlikely to require dose adjustment with travoprost/timolol
Pregnancy	Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. There are no or limited amount of data from the use of travoprost/timolol or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. Epidemiological studies have not revealed malformative effects but show 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 travoprost/timolol is administered until delivery, the neonate should be carefully monitored during the first days of life.

	Travoprost/timolol should not be used during pregnancy unless clearly necessary.
Breastfeeding	Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. It is not known whether travoprost and/or its metabolites are excreted in human milk, although in animal studies, travoprost has been shown to be excreted in milk. Because of the potential for serious adverse reactions from timolol maleate or travoprost in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Fertility	There are no data on the effects of travoprost/timolol on human fertility. Animal studies showed no effect of travoprost or timolol on fertility at doses more than 250 times the maximum recommended human ocular dose.
Paediatric patients	The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have not been established. No data are available.

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

Module SV - Post-authorisation experience

Since there are no safety concerns regarding safety and efficacy of *'[Travoprost+ Timolol] 40µg/mL + 5mg/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

'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution' is a generic formulation of *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution (Alcon Laboratories.)*

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. Travprost/timolol preservative-free eye drops solution is contained in a white plastic multi-dose container with ophthalmic dispenser.
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 dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip 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, travoprost/timolol belongs to 'Ophthalmological, beta-blocking agents' pharmacotherapeutic group (ATC code: S01ED51).
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 is a not literature finding 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.

'[Travoprost+ Timolol] 40µg/mL + 5mg/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.

Like other topically applied ophthalmic drugs, is absorbed into the systemic circulation. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of travoprost/timolol due to the beta-adrenergic component, timolol. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.
However, incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Therefore, there are 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.
Travoprost/timolol is used for treating high eye pressure and open-angle glaucoma. It is a prescription eye drop approved to decrease eye pressure in people with these conditions to help prevent damage to the optic nerve. No specific paediatric investigation plan was performed. Efficacy in paediatric patients has not been established. Therefore, a potential for off label paediatric use is limited but exists.

SVI.6 Specific paediatric issues

The SPC of the product clearly states in section 4.2 that the safety and efficacy of *'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution'* in paediatric patients have not been established. Therefore *'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free ey drops, solution'* use is not recommended in patients below the age of 18 years.

SVI.7 Conclusions

There is no safety concern related to this module.

Module SVII: Identified and potential risks

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 risks related to Travoprost

Important Identified Risk	
Macular oedema	
Frequency with 95 % CI	Not determined
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.
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 travoprost 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

Important Identified Risk	
Macular oedema	
	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	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC 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	
Hyperpigmentation	
Frequency with 95 % CI	Common (≥1/100 to <1/10)
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

Important Identified Risk	
Hyperpigmentation	
	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	In a meta-analysis of randomized controlled trials travoprost was compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension. In total, 12 articles involving 3048 patients with open-angle glaucoma or ocular hypertension were included in this meta-analysis. There was an increased incidence of pigmentation with travoprost than timolol. Travoprost 0.004% caused a higher percentage of eyelash changes than timolol, latanoprost, or travoprost 0.0015%.
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	Travoprost 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	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution*- SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC Johan W Stjernschantz, MD, PhD, Daniel M Albert, MD, Dan-Ning Hu, MD, Filippo Drago, MD, PhD, Per J

Important Identified Risk	
Hyperpigmentation	
	Wistrand, MD, PhD. Mechanism and Clinical Significance of Prostaglandin-Induced Iris Pigmentation. Survey of Ophthalmology Volume 47, Supplement 1, August 2002, Pages S162–S175 Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24 Emilio Rintaro Suzuki Jr, Cibele Lima Belico Suzuki. Efficacy and safety of travoprost alone or in combination with other agents for glaucoma and ocular hypertension: patient considerations. Clinical Ophthalmology 2010:4 1165–1171
MedDRA terms	Iris hyperpigmentation

Important Identified Risk	
Hypertrichoses	
Frequency with 95 % CI	Not determined
Seriousness/outcomes	Travoprost 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 frequently 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 PGF2α 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 PGF2α analogues. If the topically applied PGF2α analogues use in contact with the eyelids and the malar region, hypertrichosis and hyperpigmentation of the vellus hairs can occur. Discontinuation of PGF2α analogue treatment results in

Important Identified Risk	
Hypertrichoses	
	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	The mechanism of eyelash changes and their long term consequences are currently unknown.
Preventability	Not applicable.
Impact on individual patient	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. This side-effect does not have particularly deleterious physicological effects on the patients. In the female patients, the stimulation of lash growth can have a positive psychological effect, as longer thicker lashes are often considered desirable.
Potential public health impact of safety concern	There are certain undesirable physical aspects in this side effect, which can be a permanent source of nuisance, if not a real nuisance to the patient (e.g. the development of a so appreciable lengthening of the eyelashes that periodically may be necessary to cut them, unilateral use of travoprost)
Evidence source	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* - SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC 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)
MedDRA terms	Growth of eyelashes

Important Identified Risk	
Iris and uveal inflammation	
Frequency with 95 % CI	Iritis, Uveitis: Uncommon (>1/1,000 to ≤1/100)
Seriousness/outcomes	Uveitis is defined as inflammation of the uveal tract, which is further subdivided into anterior and posterior components. The anterior tract is composed of the iris and ciliary body, while the posterior tract includes choroid. Hence, uveitis is inflammation of any of these components and may also include other surrounding tissues such as sclera, retina, and optic nerve. Uveitis is often idiopathic but may be triggered by genetic, traumatic, immune, or infectious mechanisms. Uveitis, particularly posterior uveitis, is a common cause of preventable blindness, so it is deemed a sight-threatening condition. Anterior uveitis is the form most likely to present to the emergency department. When the inflammation is limited to the iris, it is termed iritis. Although normally mild and treatable, complications of iritis can include cataracts and glaucoma and it should be evaluated and treated by a health care professional.
Severity and nature of risk	Adverse event that can lead to blindness if not treated
Background incidence/prevalence	The incidence of iritis with travoprost or bimatoprost has not been studied. Only two case reports concerning the association of anterior uveitis and travoprost have been published (*Faulkner & Burk (2003)*, *Kumarasamy &* Desai (2004)). Further studies with bigger patient populations and longer follow-up periods should be conducted to establish the incidence of anterior uveitis in travoprost-treated glaucoma patients.
Risk groups or risk factors	In patients with risk factors such as a history of uveitis or prior ocular surgery.
Potential mechanisms	The mechanism by which prostaglandin analogs might cause anterior uveitis may involve the downstream stimulation of proinflammatory eicosanoids.Moreover, prostaglandin analogs can increase IL-1 and IL-6 levels in the tears, and potentially in the aqueous humor, of treated patients
Preventability	Ophthalmologist should be aware if patient has a history of uveitis or prior ocular surgery.
Impact on individual patient	Drug-induced uveitis is almost always reversible within weeks of discontinuation of the drug and treatment of the inflammation with topical corticosteroid.
Potential public health impact of safety concern	Adverse events are almost always reversible. However, if left untreated, could lead to glaucoma or blindness.
Evidence source	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC

Important Identified Risk	
Iris and uveal inflammation	
	DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution - SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24 Suominen S, Valimaki J. Bilateral anterior uveitis associated with travoprost. Acta Ophthalmol Scan 84(2): 275-6, 2006 Faulkner WJ, Burk SE. Acute anterior uveitis and corneal edema associated with travoprost. Arch Ophthalmol. 2003 Jul;121(7):1054-5. Kumarasamy M & Desai SP (2004): Anterior uveitis is associated with travoprost. BMJ 329: 205. Nikolas JS London, Sunir J Garg, Ramana S Moorthyand Emmett T Cunningham Jr. Drug-induced uveitis. London et al. Journal of Ophthalmic Inflammation and Infection 2013, 3:43
MedDRA terms	Iritis, Uveitis

Important Identified Risk	
Cardiac and vascular disorders	
Frequency with 95 % CI	Uncommon (>1/1,000 to ≤1/100)
Seriousness/outcomes	Travoprost did not cause significant reductions in systolic blood pressure during exercise and recovery as revealed from a single-center, institutional randomized, double-masked, crossover clinical trial.
Severity and nature of risk	Adverse event, related to systemic absorption of the drugs. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure), signs of deterioration of these diseases and adverse reactions may occur. Adverse events may be ocular such as bradycardia, chest pain, arrhythmia, heart block, congestive heart failure, palpitations, cardiac arrest, atrioventricular block, cardiac failure, oedema. However, systemic adverse events have also been revealed such as AV block (second- or third-degree),

Important Identified Risk	
Cardiac and vascular disorders	
	sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation.
Background incidence/prevalence	Can not be determined. Adverse event reported either from clinical trials or been reported during product use in clinical practise.
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 adirtion, 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 travoprost 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	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* – SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC Timoptol Unit Dose 0.25% and 0.5% w/v Eye Drops Solution – UK SmPC Timolol eye drops 0.5% SPC Weeranuj Yamreudeewong, PharmD, BCPS, CACP, Allison A. Dell, PharmD, Keri R. Pulley, FNP Patricia D. Stepp, MD. Asymptomatic Bradycardia Possibly Associated With Travoprost Therapy. Journal of Pharmacy Practice August 31, 2009 Philippe Denis, David Covert, Anthony Realini. Travoprost

Important Identified Risk	
Cardiac and vascular disorders	
	in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24 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	Bradycardia, arrhythmia, heart rate irregular, cardiac failure, tachycardia, chest pain, palpitations, hypertension, hypotension, oedema peripheral, congestive heart failure, atrioventricular block, cardiac arrest. Raynaud's phenomenon, cold hands and feet.

Important Identified Risk	
Respiratory disorders	
Frequency with 95 % CI	Uncommon (>1/1,000 to ≤1/100)
Seriousness/outcomes	Travoprost 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

Important Identified Risk	
Respiratory disorders	
	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	Topical applied prostaglandin analogues should be avoided in patients with severe corticodependent asthma. Treartment should also be avoided in patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, or a history of bronchial asthma, due to timolol component
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 severe corticodependent asthma should be advised not to take this product. In general, patients at risk should follow treatment only if the potential benefit

Important Identified Risk	
Respiratory disorders	
	outweighs the potential risk
Impact on individual patient	Potential adrevrse events: *Travoprost:* Dysponea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation *Timolol:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease) *Combination:* Dyspnoea, postnasal drip, dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort, asthma.
Potential public health impact of safety concern	Potentially life threatening
Evidence source	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* - SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 *Travatan 40 micrograms/mL eye drops, solution* – SPC Timoptol Unit Dose 0.25% and 0.5% w/v Eye Drops Solution – UK SmPC Timolol eye drops 0.5% SPC 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 and metabolism of timolol in human ocular tissue, Academic dissertation

Important Identified Risk	
Respiratory disorders	
	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	Dyspnoea, postnasal drip, dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort, asthma.

Important identified risks related to Timolol

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

Important identified Risk	
Corneal toxicity – dry eye	
	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	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'* SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* - SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 Timoptol Unit Dose 0.25% and 0.5% w/v Eye Drops Solution – UK SmPC Timolol eye drops 0.5% SPC Herreras JM, Pastor JC, Calonge M, Asensio VM., Ocular surface alteration after long-term treatment with an antiglaucomatous drug. Ophthalmology. 1992 Jul; 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	dry eye

Important potential risks

Important Potential Risk	
Ocular and skin melanomas	
Frequency with 95 % CI	Common (>1/100 to <1/10)
Seriousness/outcomes	Ocular melanoma, or melanoma of the eye, is the most common primary eye tumor in adults with around 2,000 new

Important Potential Risk	
Ocular and skin melanomas	
	cases diagnosed each year in the United States. Like other melanomas, it begins in melanocytes – the cells that produce the pigment melanin that colors the skin, hair, and eyes, as well as well as forms moles.
Severity and nature of risk	Iris melanomas have relatively good outcomes with a 5-year survival rate of more than 95%. They are predominantly of the spindle-cell type and are usually smaller in size than posterior melanomas because of earlier detection. Conservative management is generally advocated whenever possible, but surgical intervention may be justified with unequivocal tumor growth or with extensive disease at initial examination.
Background incidence/prevalence	Eyes mixed-colour irides containing brown areas are especially susceptible to colour change. More than three-quarters of green-brown and yellow-brown irides treated with latanoprost were found to be affected. Iris darkening in blue-grey or brown irides is rare, or less visible. After six to twelve months of travoprost treatment, the incidence of iris colour change (independent of iris colour) varied between 1.0% and 3.1%. At the same length of treatment, iris darkening was noted in 5.1% to 10.1% of eyes for latanoprost users and in 1.1% to 1.5% for bimatoprost users
Risk groups or risk factors	Some studies suggest that fair skin type is a risk factor for ocular melanoma.
Potential mechanisms	Darkening of the iris is an irreversible side effect of all topical PGF2α analogues. Iris darkening is caused by increased transcription and increased activity of tyrosinase in the iris stromal melanocytes, which is stimulated by clinical dosage of topical PGF2α analogues. Iris darkening does not involve mitotic activity of the melanocytes; thus it does not represent an increased risk for development or progression of uveal malignant melanoma.
Preventability	Patients with fair skin type should be closely monitoring.
Impact on individual patient	Deterioration of patient life
Potential public health impact of safety concern	Potentially sight-threatening side effects.
Evidence source	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution* - SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006

Important Potential Risk	
Ocular and skin melanomas	
	Ocular Melanoma - Melanoma Research Foundation Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book) Albert Alm, Ian Grierson, M. Bruce Shields. Side Effects Associated with Prostaglandin Analog Therapy Survey of Ophthalmology Volume 53, Issue 6, Supplement, November 2008, Pages S93–S105 Intraocular (Uveal) Melanoma Treatment - National Cancer Institute
MedDRA terms	NA

Important Potential Risk	
Use during pregnancy and lactation	
Frequency with 95 % CI	Unknown
Seriousness/outcomes	In ocular toxicity studies in monkeys, administration of Travoprost at a dose of 0.45 microgram, twice a day, was shown to induce increased palpebral fissure. Topical ocular administration of Travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of Travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^{3}H-Travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).
Severity and nature of risk	Potential teratogenicity *(*increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly*).* However, some experts have claimed that

Important Potential Risk	
Use during pregnancy and lactation	
	latanoprost and travoprost have insufficient active ingredients to cause adverse effects on the foetus.
Background incidence/prevalence	Not determined.
Risk groups or risk factors	Women of child bearing age/potential, in pregnancy and during lactation
Potential mechanisms	Travoprost is a prodrug that will hydrolyse in the cornea to become fluprostenol—a type of prostaglandin that is highly selective for F2α receptors, which is used to induce abortion in animals by causing uterine smooth muscle contractions.
Preventability	Travoprost must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place. In addition, Travoprost should not be used during pregnancy unless clearly necessary neither in breast-feeding mothers. In case that any of the product comes into contact with the skin then it should be washed off straight away.
Impact on individual patient	Harmful pharmacological effects on pregnancy and/or the foetus/new-born child.
Potential public health impact of safety concern	Potential teratogenicity
Evidence source	*'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, eye drops, solution'*- SmPC *DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution*- SmPC *DuoTrav™*- product Monograph. Alcon Canada Inc. March 2006 CY Chung, AKH Kwok, KL Chung. Use of ophthalmic medications during Pregnancy. Hong Kong Med J Vol 10 No 3 June 2004
MedDRA terms	NA

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Pharmacodynamic drug interactions
Travoprost is unlikely to interact adversely with other glaucoma agents or with other receptor mediated pharmacologic agents. Drug interactions of timolol are typical of nonselective beta adrenergic antagonists and are well defined in the scientific literature.

Potential pharmacokinetic interactions between active ingredients are unlikely, since travosprost and timolol undergo different metabolic pathways and also taking into account the low systemic levels achieved following topical ocular administration.

Pharmacokinetic interaction studies
No studies evaluating drug-drug interactions have been performed. Since travoprost undergoes a biotransformation pathway similar to endogenous prostaglandin-F2α, and since systemic levels of active metabolite following topical ocular administration are negligible, interactions with concomitant medications in patients receiving topical ocular doses is considered to be unlikely. In vitro experiments have shown travoprost free acid to be moderately bound (about 80%) to plasma proteins in humans, indicating drug-drug interactions through protein binding to be unlikely.

Specific drug interaction studies with cytochrome P450 substrates have not been conducted with AL-5848. The very low systemic exposure to AL-5848 after topical ocular administration of travoprost would not influence the P450 enzyme-mediated metabolism of other concomitant agents. Concomitant administration of potent inhibitors of cytochrome P450 enzymes would not impact the low systemic exposure of AL-5848 after topical ocular administration of travoprost/timolol Eye Drops, since travoprost is metabolized extensively by routes other than cytochrome P450 pathways.

Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during coadministration of oral timolol with quinidine, possibly because of quinidine inhibiting the metabolism of timolol by the cytochrome P450 CYP2D6.

SVII.4.2 Important identified and potential interactions

Drug-Drug Interactions

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and travoprost/timolol should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

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

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

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

CNS Depressants: Although specific drug interaction studies have not been conducted with travoprost/timolol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Tricyclic Antidepressants: Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with travoprost/timolol can lead to an interference in IOP lowering effect.

No data are available on the level of circulating catecholamines after travoprost/timolol is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Epinephrine: Mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.

Drug-Lifestyle Interactions

Effects on the Ability to Drive and Use Machines
As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

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, hypertrichoses, iris and uveal inflammation, macular oedema 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 cardiac and vascular disorders as well as corneal toxicity.

SVII.5.2 Important pharmacological class effects not discussed above

Adverse drug reactions associated with the use of beta blockers not discussed above include hypoglycaemia, systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis and choroidal detachment.

Module SVIII: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye
Important potential risks	• Ocular and skin melanomas • Use during pregnancy and lactation
Missing information	• Potential interactions • Exposure in paediatric population

Part III: PHARMACOVIGILANCE PLAN

Routine pharmacovigilance Activities

'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution' is a generic formulation. Therefore, routine pharmacovigilance activities allows a post-approval safety monitoring, such as: collection of all reported ADRs, submission to competent authorities according to regulations in force, literature screening, redaction of Periodic Safety Update Reports, continuous monitoring of the safety profile of the products including signal detection, and pregnancy report form when applicable.

No additional Pharmacovigilance activities are established.

III.1 Safety concerns and overview of planned pharmacovigilance actions

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

Macular oedema		
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

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

Hypertrichoses		
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

Iris and uveal inflammation		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**

Iris and uveal inflammation		
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

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

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

Ocular and skin melanomas		
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

Potential interactions		
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

Exposure in paediatric patients		
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

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

'[Travoprost+ Timolol] 40µg/mL + 5mg/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 travoprost/ timolol combination 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	**Macular oedema**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning macular oedema occurrence already included in sections 4.4 and 4.8 of the SPC. In addition is listed in section 4 of PIL (risk communication to reduce the incidence of it ***Section 4.4:*** *Macular oedema has been reported during treatment with prostaglandin F2α analogues. Caution is recommended when using [Invented name] in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.* ***Section 4.8:*** *Adverse reactions observed in clinical studies or with post-marketing experience* *<u>Ocular:</u>* *Not known: macular oedema*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks.
Planned dates for assessment	Assessment takes place routinely through the

Important identified risk	
	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	**Hyperpigmentation**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning hyperpigmentation already included in sections 4.4 and 4.8 of the SPC. In addition is listed in sections 2 and 4 of PIL (risk communication to reduce the incidence of it ***Section 4.4:*** *Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. 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. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.* *In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.* *In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of Travoprost has been reported in 0.4% of*

Important identified risk	
	patients. ***Section 4.8:*** *Additional adverse reactions that have been seen with one of the active substances and may potentially occur:* *Travoprost* *<u>Eyes disorders:</u> iris hyperpigmentation* *<u>Skin and subcutaneous tissue disorders:</u> hyperpigmentation (periocular)*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**Hypertrichoses**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning hypertrichosis already included in sections 4.4 and 4.8 of the SPC. In addition is listed in sections 2 and 4 of PIL (risk communication to reduce the incidence of it ***Section 4.4:*** *Travoprost 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,*

Important identified risk	
	pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long term consequences are currently unknown. ***Section 4.8:*** *<u>Skin and subcutaneous tissue disorders:</u>* *Uncommon: hypertrichosis*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**Iris and uveal inflammation**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning occurrence of iritis and uveitis already included in sections 4.4 and 4.8 of the SPC. In addition is listed in section 4 of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *In patients with known predisposing risk factors for iritis/uveitis, travoprost/timolol can be used with caution.* ***Section 4.8:*** *<u>Eye disorders:</u>* *Uncommon: keratitis, iritis, conjunctivitis,*

Important identified risk	
	anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes eye allergy, conjunctival oedema, eyelid oedema. *Additional adverse reactions that have been seen with one of the active substances and may potentially occur:* *Travoprost* *Eyes disorders: uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation.*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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 concerning cardiac and vascular disorders already included in sections 4.4 and 4.8 of the SPC. In addition is listed in sections 2 and 4 of PIL (risk communication to reduce the incidence of it)

Important identified risk	
	Section 4.4: <u>*Cardiac disorders:*</u> *In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.* *Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.* <u>*Vascular disorders:*</u> *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:*** <u>*Cardiac disorders:*</u> *Uncommon: bradycardia* *Rare: arrhythmia, heart rate irregular* *Not known: cardiac failure, tachycardia, chest pain, palpitations* *Vascular disorders:* *Uncommon: hypertension, hypotension* *Not known: oedema peripheral* *Additional adverse reactions that have been seen with one of the active substances and may potentially occur:* *Timolol* <u>*Cardiac disorders:*</u> *Chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest.* <u>*Vascular disorders:*</u> *Raynaud's phenomenon, cold hands and feet.*

Important identified risk	
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**Respiratory disorders**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning concerning respiratory disorders already included in sections 4.4 and 4.8 of the SPC. In addition is listed in sections 2 and 4 of PIL (risk communication to reduce the incidence of it) ***Section 4.4:*** *Respiratory disorders:* *Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.* *Travoprost/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.* ***Section 4.8:*** *Respiratory, thoracic and mediastinal*

Important identified risk	
	disorders: *Uncommon: dyspnoea, postnasal drip* *Rare: dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort* *Not known: asthma* *Additional adverse reactions that have been seen with one of the active substances and may potentially occur:* *Timolol* *Respiratory, thoracic and mediastinal disorders:* *Bronchospasm (predominantly in patients with pre-existing bronchospastic disease*).
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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 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)

Important identified risk	
	Section 4.4: *Corneal diseases:* *Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.* ***Section 4.8:*** *Eye disorders:* *Rare: corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis* *Not known: macular oedema, eyelid ptosis, corneal disorder*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**Ocular and skin melanomas**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk

Important potential risk	
Routine risk minimisation measures	Warning concerning ocular and skin melanomas already included in section 4.8 of SmPC. In addition is a listed in section 4 of the PIL (risk communication to reduce the incidence of it) ***Section 4.8:*** *Additional adverse reactions that have been seen with one of the active substances and may potentially occur:* *Travoprost* *Eye disorders: uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation.*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**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:***

Important potential risk	
	Women of childbearing potential/contraception *Travoprost/timolol must not be used in women who may become pregnant unless adequate contraceptive measures are in place.* *Pregnancy* *Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child.* *There are no or limited amount of data from the use of travoprost/timolol or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.* *Epidemiological studies have not revealed malformative effects but show 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 travoprost/timolol is administered until delivery, the neonate should be carefully monitored during the first days of life.* *Travoprost/timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.* *Breastfeeding* *It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk having the potential to cause serious adverse reactions in the breastfeeding infant. 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,*

Important potential risk	
	see section 4.2. *The use of travoprost/timolol by breast-feeding women is not recommended.*
	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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of these identified risks. No safety action of competent authorities related to these risks
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	**Potential interactions**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the lack of specific drug interaction studies already included in section 4.5 of SmPC. In addition is a listed in section 2 of the PIL (risk communication to reduce the incidence of it) ***Section 4.5:*** *No interaction studies have been performed.*
	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	The Applicant will evaluate the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed	No increase in frequency of spontaneous

Missing information	
risk minimisation measures	reports of this missing information. No safety action of competent authorities related to these risks
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	**Exposure in paediatric patients**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Information 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:*** <u>*Paediatric Population*</u> *The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have 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	The Applicant will evaluate 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	No increase in frequency of spontaneous reports of this missing information. No safety action of competent authorities related to these risks
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

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
Macular oedema	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None
Hyperpigmentation	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Hypertrichoses	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Iris and uveal inflammation	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None
Cardiac and vascular disorders	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Respiratory disorders	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Corneal toxicity – dry eye	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None
Ocular and skin melanomas	SmPC section 4.8 PIL section 4 Prescription only medicine	None
Use during pregnancy and lactation	SmPC section 4.6 PIL section 2 Prescription only medicine	None
Potential interactions	SmPC section 4.5 PIL section 2 Prescription only medicine	None
Exposure in paediatric population	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	• Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye
Important potential risks	• Ocular and skin melanomas • Use during pregnancy and lactation
Missing information	• Potential interactions • Exposure in paediatric population

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**
Macular oedema	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None
Hyperpigmentation	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Hypertrichoses	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Iris and uveal inflammation	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None

Cardiac and vascular disorders	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Respiratory disorders	SmPC sections 4.4, 4.8 PIL sections 2, 4 Prescription only medicine	None
Corneal toxicity – dry eye	SmPC sections 4.4, 4.8 PIL section 4 Prescription only medicine	None
Ocular and skin melanomas	SmPC section 4.8 PIL section 4 Prescription only medicine	None
Use during pregnancy and lactation	SmPC section 4.6 PIL section 2 Prescription only medicine	None
Potential interactions	SmPC section 4.5 PIL section 2 Prescription only medicine	None
Exposure in paediatric population	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

Studies estimated 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. In approximately 3% of people with ocular hypertension, could lead to vision loss.

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 the second leading cause of blindness in the world (after cataracts) and the leading cause of blindness among African-Americans. **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 estimated that there are 44.7 million

people with open-angle glaucoma worldwide in 2010, and that this number will increase to 58.6 million in 2020. It is estimated that there are 2.8 million people with open-angle glaucoma in the United States in 2010, and that the number will increase to 3.4 million in 2020.
The Barbados Eye Study found ocular hypertension present more frequently in women. Mean intraoccular 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. Black subjects had almost 3 times the age-adjusted prevalence of glaucoma than white subjects.

VI.2.2 Summary of treatment benefits

Drugs to treat glaucoma are classified by their active ingredient. These include: prostaglandin analogs, beta blockers, alpha agonists, carbonic anhydrase inhibitors and combination drugs like travoprost/timolol.

Travoprost is a highly potent and efficacious compound for lowering intraocular pressure as both a monotherapy agent as well as in combination with other drugs. Additional efficacy in African Americans is a particularly important benefit since this group of patients often demonstrates the most advanced, aggressive form of disease.

The majority of the randomized controlled trials have found travoprost to be equally efficacious in comparison with latanoprost and bimatoprost in eyes with ocular hypertension and primary open angle glaucoma.

Recent trials have suggested that travoprost has a robust effect in lowering of intraocular pressure with little diurnal fluctuation, which can last beyond the standard dosing interval of 24 hours. Other pilot trials suggested that the travoprost effect can continue up to 84 hours after the final dose.

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

Beta blockers such as timolol are the second most often used class of medication and work by decreasing production of fluid from the eye. They have systemic side effects that can be minimized by closing the eyes following application or using a technique called punctual occlusion that prevents the drug from entering the tear drainage duct and systemic circulation.

There are many studies comparing safety and efficacy of timolol maleate with other drugs using to treat glaucoma. Timolol has been shown safe and effective alone or in combination formulations.

VI.2.3 Unknowns relating to treatment benefits

In the SmPC of *'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free eye drops, solution'* is stated that efficacy of the product in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

In addition, interaction studies of travoprost with other medicinal products are not available

VI.2.4 Summary of safety concerns

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**
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. Light rays are focused onto the retina, where they are transmitted to the brain and interpreted as the images seen. It is the macula that is responsible for pinpoint vision, allowing reading, sewing or recognizing a face. 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
Change in the colour of iris (the coloured part of the eye) *(Hyperpigmentation)*	Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. 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.	You should advise with an ophthalmologist however these changes are solely cosmetic in nature, and have not posed a health risk in any form.
Increase of the length, thickness, colour and/or number of the eyelashes that may cause unusual hair growth on the eyelids *(Hypertrichoses)*	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. This side-effect does not have particularly deleterious pshysicological effects on the patients.	You should advise with an ophthalmologist however, these changes are solely cosmetic in nature.

Pain, sensitivity to light, blurred vision, and redness *(Iris and uveal inflammation)*	Uveitis and iritis are known adverse effects of travoprost (prostaglandin F2 analogues adverse event) and are most common with latanoprost. Iritis is a serious condition that, if left untreated, could lead to glaucoma or blindness.	Drug-induced uveitis is almost always reversible within weeks of discontinuation of the drug and treatment of the inflammation with topical corticosteroid. An ophthalmologist should immediately be advised.
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 disease	Yes, by consultation of a doctor.
Breathlessness or wheezing or increase of asthma symptoms *(Respiratory disorders)*	Respiratory disorders are adverse event related to systemic absorption of the drug. Travoprost/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.
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.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Ocular and skin melanomas	Ocular melanoma, or melanoma of the eye, is the most common primary eye tumor in adults with around 2,000 new cases diagnosed each year in the United States. Like other melanomas, it begins in melanocytes – the cells that produce

	the pigment melanin that colors the skin, hair, and eyes, as well as form moles. Ocular melanoma accounts for approximately 5-12% of all melanoma cases. Some studies suggest that fair skin type is a risk factor for ocular melanoma.
Use during pregnancy and lactation	*Travoprost* Topical ocular administration of travoprost to monkeys, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml). *Timolol* Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).

Missing information	
Risk	**What is known**
Potential interactions	Interaction studies with other medicinal products and other forms of interation have not been performed.
Exposure in paediatric population	The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have 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	26.09.2016	**Important identified risks** • Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information** • Potential interactions • Exposure in paediatric population	Initial version

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] 40 micrograms/mL + 5 mg/mL eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).

Excipients with known effect
Each mL of solution contains 2 mg of macrogolglycerol hydroxystearate 40 and 7.5 mg of propylene glycol (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

Clear, colorless aqueous solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] is indicated in adults for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (see section 5.1).

4.2 Posology and method of administration

Posology
Use in adults, including the older population

The dose is one drop of [Invented name] in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day.

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

Special Populations

Hepatic and renal impairment

No studies have been conducted with travoprost/timolol or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment.

Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dose adjustment was necessary in these patients.

Patients with hepatic or renal impairment are unlikely to require dose adjustment with [Invented name] (see section 5.2).

Paediatric population

The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

For ocular use.

The patient should remove the protective overwrap immediately prior to initial use.

[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.

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 (see section 4.4).

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5).

When substituting another ophthalmic antiglaucoma medicinal product with [Invented name], the other medicinal product should be discontinued and [Invented name] should be started the following day.

Patients must be instructed to remove soft contact lenses prior to application of [Invented name] and wait 15 minutes after instillation of the dose before reinsertion (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other beta-blockers.
- Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.
- Severe allergic rhinitis and corneal dystrophies.

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicinal products may occur. The 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

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, 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-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Muscle weakness

Beta-adrenergic blocking medicinal products have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness).

Corneal diseases

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

Choroidal detachment

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

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 medicinal product. 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).

Surgical anaesthesia

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

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Skin contact

Prostaglandins and prostaglandin analogues are biologically active substances that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

Anaphylactic reactions

While taking beta-blockers, patients with 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.

Concomitant therapy

Timolol may interact with other medicinal products (see section 4.5).

The use of two local prostaglandins is not recommended.

Ocular effects

Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. 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. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues.

Travoprost 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. The mechanism of eyelash changes and their long term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific.

There is no experience of travoprost/timolol in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma.

Macular oedema has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. Caution is recommended when using [Invented name] in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, and in patients with active intraocular inflammation, [Invented name] can be used with caution.

Excipients

[Invented name] contains macrogolglycerol hydroxystearate 40 which may cause skin reactions.

[Invented name] contains propylene glycol which may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with travoprost or timolol.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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

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

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

Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicinal products.

Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

[Invented name] must not be used in women who may become pregnant unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child.

There are no or limited amount of data from the use of travoprost/timolol or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but show 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.

[Invented name] should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Breastfeeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk having the potential to cause serious adverse reactions in the breastfeeding infant. 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.

The use of [Invented name] by breast-feeding women is not recommended.

Fertility

There are no data on the effects of travoprost/timolol on human fertility. Animal studies showed no effect of travoprost or timolol on fertility at doses more than 250 times the maximum recommended human ocular dose.

4.7 Effects on ability to drive and use machines

[Invented name] has no or negligible influence on the ability to drive and use machines.

As with any eye drop, temporary blurred vision or other visual disturbances may occur. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2170 patients treated with travoprost/timolol the most frequently reported treatment-related adverse reaction was ocular hyperaemia (12.0%).

Tabulated summary of adverse reactions

The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

System Organ Class	**Frequency**	**Adverse Reactions**
Immune system disorders	Uncommon	hypersensitivity.
Psychiatric disorders	Rare	nervousness.
	Not known	depression.
Nervous system disorders	Uncommon	dizziness, headache.
	Not known	cerebrovascular accident, syncope, paraesthesia.
Eye disorders	Very common	ocular hyperaemia
	Common	punctate keratitis, eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation.
	Uncommon	keratitis, iritis, conjunctivitis, anterior

		chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes eye allergy, conjunctival oedema, eyelid oedema.
	Rare	corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis.
	Not known	macular oedema, eyelid ptosis, corneal disorder.
Cardiac disorders	Uncommon	bradycardia.
	Rare	arrhythmia, heart rate irregular
	Not known	cardiac failure, tachycardia, chest pain palpitations.
Vascular disorders	Uncommon	hypertension, hypotension.
	Not known	oedema peripheral
Respiratory, thoracic and mediastinal disorders	Uncommon	dyspnoea, postnasal drip.
	Rare	dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort
	Not known	asthma.
Gastrointestinal disorders	Not known	dysgeusia
Hepatobiliary disorders	Rare	alanine aminotransferase increased, aspartate aminotransferase increased.
Skin and subcutaneous tissue disorders	Uncommon	dermatitis contact, hypertrichosis
	Rare	urticaria, skin discolouration, alopecia, skin hyperpigmentation (periocular).

	Not known	rash.
Musculoskeletal and connective tissue disorders	Rare	pain in extremity.
Renal and urinary disorders	Rare	chromaturia.
General disorders and administration site conditions	Rare	thirst, fatigue.

Additional adverse reactions that have been seen with one of the active substances and may potentially occur with [Invented name]:

Travoprost

System Organ Class	**MedDRA preferred Term**
Eye disorders	uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation.
Skin and subcutaneous tissue disorders	skin exfoliation.

Timolol

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Additional listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

System Organ Class	**MedDRA preferred Term**
Immune system disorders	Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis.
Metabolism and nutrition disorders	Hypoglycaemia.
Psychiatric disorders	Insomnia, nightmares, memory loss.

Nervous system disorders	Cerebral ischaemia, increases in signs and symptoms of myasthenia gravis.
Eye disorders	Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, diplopia.
Cardiac disorders	Chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest.
Vascular disorders	Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic and mediastinal disorders	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease).
Gastrointestinal disorders	Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders	Psoriasiform rash or exacerbation of psoriasis.
Musculoskeletal and connective tissue disorders	Myalgia.
Reproductive system and breast disorders	Sexual dysfunction, decreased libido.
General disorders and administration site conditions	Asthenia.

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.

In case of accidental ingestion, symptoms of overdose from systemic beta blockade may include bradycardia, hypotension, bronchospasm and heart failure.

If overdose with [Invented name] occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, ATC code: S01ED51.

Mechanism of action

[Invented name] contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost, a prostaglandin $F_{2\alpha}$ analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Secondary pharmacology

Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily).

Pharmacodynamic effects

Clinical effects

In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of travoprost/timolol dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of travoprost/timolol as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

In a three-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg, the mean IOP-lowering effect of travoprost/timolol dosed once-daily in the morning was 9 to 12 mmHg, and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in morning mean IOP (8AM-24 hours after the last dose of travoprost/timolol) was observed compared to travoprost at all visits throughout the study.

In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 23 to 26 mmHg, the mean IOP-lowering effect of travoprost/timolol dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once-daily in the evening and timolol 5 mg/ml dosed once-daily in the morning.

In a 6-week, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 24 to 26 mmHg, the mean IOP-lowering effect of travoprost/timolol (polyquaternium-1-preserved) dosed once-daily in the morning was 8 mmHg and equivalent to that of travoprost/timolol (benzalkonium chloride-preserved).

Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of travoprost/timolol included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion.

Existing data suggest that evening dosing might have some advantages in the mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of travoprost/timolol PQ in healthy subjects (N=22) for 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (94.4%) and generally was not detectable one hour after dosing. When measurable (≥ 0.01 ng/ml, the assay limit of quantitation), concentrations ranged from 0.01 to 0.03 ng/ml. The mean timolol steady-state C_{max} was 1.34 ng/ml and T_{max} was approximately 0.69 hours after once-daily administration of travoprost/timolol.

Distribution

Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration of travoprost/timolol.

Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to 12 hours after ocular administration of travoprost/timolol.

Biotransformation

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin $F_{2\alpha}$ which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma $t_{1/2}$ of timolol is 4 hours after ocular administration of travoprost/timolol.

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2% of an ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

5.3 Preclinical safety data

In monkeys, administration of travoprost/timolol twice–daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids.

Travoprost/timolol preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

Travoprost

Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity.

Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered 3H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in

rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).

Timolol

Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate (nominal value:40)
Sodium chloride
Propylene glycol
Boric Acid
Mannitol
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months
[Invented name] eye drops solution should be used no longer than 28 days after first opening of the multi – dose container

6.4 Special precautions for storage

Before opening, the bottle should be kept in overwrap pouch in order to protect from moisture.
After first opening, this medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

In a cardboard box, a 5 ml white plastic multi-dose container with ophthalmic dispenser containing 2.5 mL of the ophthalmic solution is included.
The multi-dose container can be available in an overwrap, inside the cardboard box.

The product is available in the following pack sizes:

Cartons containing 1 or 3 number of bottles.

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] 40 micrograms/mL+ 5 mg/mL eye drops, solution
travoprost/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 or pharmacist.
- 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 or pharmacist. 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] eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

[Invented name] eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.

[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 travoprost, timolol, or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any prostaglandins or beta-blockers

- if you have now or have had in the 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, or other types of breathing problems
- if you have severe hay fever
- if you have a slow heart beat, heart failure or disorders of heart rhythm (irregular heart beats)
- if the surface of your eye is cloudy

Ask your doctor for advice if any of these apply to you.

Warnings and precautions

Talk to your doctor or pharmacist 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)
- diabetes, as timolol may mask signs and symptoms of low blood sugar
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- myasthenia gravis (chronic neuromuscular weakness)
- any severe allergic reaction (skin rash, redness and itching of the eye) while using [Invented name], whatever the cause, adrenaline treatment may not be as effective. So when receiving any other treatment please tell the doctor that you are using [Invented name]
- a cataract surgery
- an eye inflammation

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

[Invented name] may change the colour of your iris (the coloured part of your eye). This change may be permanent.

[Invented name] may increase the length, thickness, colour and/or number of your eyelashes and may cause unusual hair growth on your eyelids.

Travoprost may be absorbed through the skin and therefore should not be used by women who are pregnant or are attempting to become pregnant. If any of the medicine comes into contact with the skin then it should be washed off straight away.

Children

[Invented name] is not to be used by children and adolescents under 18 years of age.

Other medicines and [Invented name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

[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 if you are using or intend to use

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

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use [Invented name] if you are pregnant unless your doctor considers it necessary. If you could get pregnant you must use adequate contraception whilst you use the medicine.

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

Driving and using machines

You may find that your vision is blurred for a time just after you use [Invented name]. Do not drive or use machines until this has worn off.

[Invented name] contains macrogolglycerol hydroxystearate 40 and propylene glycol which may cause skin reactions and irritation.

3. How to use [Invented name]

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

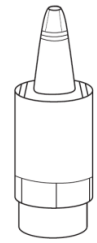
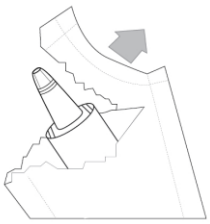
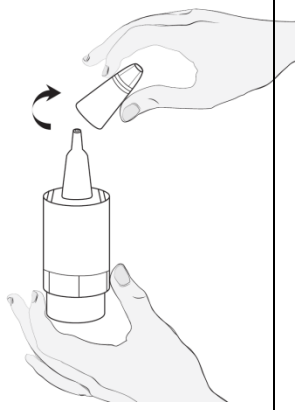
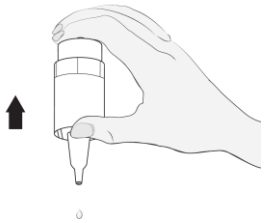
The recommended dose is

One drop in the affected eye or eyes, once a day-in the morning or in the evening. Use at the same time each day.

Only use [Invented name] in both eyes if your doctor told you to do so. Use it for as long as your doctor told you to.

Only use [Invented name] for dropping in your eyes.

Instructions for use

<table>
<tr>
<td> 
1a
 
1b
 
1c</td>
<td>• Take the multi-dose container **(picture 1a)** out of the carton box. If the container is stored within an overwrap pouch, tear – off to open **(picture 1b)** and write the date of opening on the carton box and the bottle in the space provided.
• Get the medicine bottle and a mirror.
• Wash your hands.
• Remove the cap **(picture 1c)**.</td>
</tr>
<tr>
<td> 
2</td>
<td>• Hold the bottle upside down with the thumb on the shoulder of the bottle and the other fingers on the bottom of the bottle. Before the first use, pump the bottle repeatedly, approximately 10 times, until the first drop emerges **(picture 2)**.</td>
</tr>
</table>

 **3**	• Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here **(picture 3)**. • Bring the bottle tip close to the eye. Use the mirror if it helps.
 **4**  **5**	• **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops. • Gently press down on the bottom side of the bottle to release one drop of medicine at a time **(picture 4)**. • If a drop misses your eye, try again. • After using the medicine, press a finger into the corner of your eye, by the nose **(picture 5)**. This helps to stop the medicine getting into the rest of the body.
	• If you use drops in both eyes, repeat these same steps for your other eye. • Close the multi-dose container cap firmly immediately after use. • Only use one bottle of medicine at a time. Do not open the cap until you need to use the multi-dose container. • **You must throw away the bottle 28 days after you first opened it,** to prevent infections, and use a new bottle.

If you use more [Invented name] than you should

If you use more [Invented name] than you should, rinse it all out with warm water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use [Invented name]

If you forget to use [Invented name], continue with the next dose as planned. Do not use a double dose to make up for a forgotten dose. The dose should not exceed one daily drop in the affected eye(s).

If you stop using [Invented name]

If you stop using [Invented name] without speaking to your doctor the pressure in your eye will not be controlled which could lead to loss of sight.

If you are using other eye drops, leave at least 5 minutes between putting in [Invented name] and the other drops.

If you wear soft contact lenses do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

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

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.

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

Effects in the eye: eye redness

Common (may affect up to 1 in 10 people):

Effects in the eye: eye surface inflammation with surface damage, eye pain, blurred vision, abnormal vision, dry eye, itchy eye, eye discomfort, signs and symptoms of eye irritation (e.g. burning, stinging).

Uncommon (may affect up to 1 in 100 people):

Effects in the eye: inflammation of the eye surface, inflammation of the eyelid, swollen conjunctiva, increased growth of eyelashes, iris inflammation, eye inflammation, sensitivity to light, reduced vision, tired eyes, eye allergy, eye swelling, increased tear production, eyelid redness, eyelid colour change

General side effects: drug allergy, dizziness, headache, increased or decreased blood pressure, shortness of breath, excessive hair growth, drip at back of throat, skin inflammation and itching, decreased heart rate.

Rare side effects (may affect up to 1 in 1,000 people):

Effects in the eye: thinning of the eye surface, inflammation of the eyelid glands, broken blood vessel in the eye, eyelid crusting, abnormally positioned eyelashes, abnormal growth of lashes.

General side effects: nervousness, irregular heart rate, loss of hair, voice disorders, difficulty breathing, cough, throat irritation, hives, abnormal liver blood tests, skin discolouration, skin darkening, thirst, tiredness, discomfort inside of nose, coloured urine, pain in hands and feet.

Not known (frequency cannot be estimated from the available data):
Effects in the eye: droopy eyelid (making the eye stay half closed)

General side effects: rash, heart failure, chest pain, stroke, fainting, depression, asthma, increased heart rate, numbness or tingling sensation, palpitations, swelling in the lower limbs, bad taste.

Additionally:

[Invented name] is a combination of 2 active substances. Like other medicines applied into eyes, travoprost and timolol (a beta-blocker) are absorbed into the blood. This may cause similar side effects as seen with intraveneous and/or oral beta-blocking medicines. The incidence of side effects after topical ophthalmic administration is lower than when medicines are, for example, taken by mouth or injected. Listed side effects which include reactions seen within the class of beta-blockers when used for treating eye conditions are as follows:

Effects in the eye: inflammation of the eyelid, inflammation in the cornea, detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity, corneal erosion (damage to the front layer of the eyeball), double vision, changes in the colour of the iris

General side effects:

- Heart and circulation: slow heart rate, palpitations, oedema (fluid build up), changes in the rhythm or speed of the heartbeat, congestive heart failure (heart disease with shortness of breath and swelling of the feet and legs due to fluid build up), a type of heart rhythm disorder, heart attack low blood pressure, Raynaud's phenomenon, cold hands and feet, reduced blood supply to the brain.

- Respiratory: constriction of the airways in the lungs (predominantly in patients with pre-existing disease), difficulty breathing, stuffy nose

- Nervous system and general disorders: difficulty sleeping (insomnia), nightmares, memory loss loss of strength and energy

- Gastric: taste disturbances, nausea, indigestion, diarrhea, dry mouth, abdominal pain, vomiting

- Allergy: generalized allergic reactions including swelling beneath the skin that can occur in areas such as the face and limbs, and can obstruct the airway which may cause difficulty swallowing or breathing, localized and generalized rash, itchiness, severe sudden life-threatening allergic reaction.

- Skin: skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, peeling skin

- Muscular: increases in signs and symptoms of myasthenia gravis (muscle disorder), unusual sensations like pins and needles, muscle weakness/tiredness, muscle pain not caused by exercise

- Reproduction: sexual dysfunction, decreased libido

- Metabolism: low blood sugar levels

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 carton and bottle after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the multi dose container has been broken or damaged before you first open it.

This medicinal product does not require any special temperature storage conditions.

You must throw away the bottle 28 days after you first opened it, to prevent infections, and use a new bottle. Write down the date you opened the bottle in the space the bottle label and box.

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 travoprost and timolol.

Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).

- The other ingredients are mannitol, boric acid, sodium hydroxide, macrogolglycerol hydroxystearate (nominal value: 40), propylene glycol, sodium chloride and water purified.

What [Invented name] looks like and contents of the pack

[Invented name] eye drops, solution is presented as a 2.5 ml clear, colorless, aqueous solution in a cardboard box containing a 5 ml white plastic multi-dose container.

The multi – dose container can be available in an overwrap, inside the cardboard box.

The product is available in the following pack sizes:

Cartons containing 1 or 3 number of 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)

1. Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol*. Aug 1997;115(8):1051-7.

2. Chihara E. Assessment of true intraocular pressure: the gap between theory and practical data. *Surv Ophthalmol*. May-Jun 2008;53(3):203-18.

3. 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.

4. 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.

5. Annette Giangiacomo, Anne Louise Coleman, The Epidemiology of Glaucoma Chapter 2

6. Murray F, American Optometric Association-OAG

7. Jerald A Bell, MD, Ocular Hypertension
8. http://www.emedicinehealth.com/ocular_hypertension

9. 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

10. Mukhtar Bizrah, Li Guo, Maria Francesca Cordeiro. Glaucoma and Alzheimer's Disease in the Elderly. Aging Health. 2011;7(5):719-733

11. Anne Chang-Godinich, Ocular hypertension medications. http://emedicine.medscape.com

12. 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

13. '[Travoprost+ Timolol] 40µg/mL + 5µg/mL, eye drops, solution'- SmPC

14. DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution – SmPC

15. DuoTravTM- product Monograph. Alcon Canada Inc. March 2006

16. Travatan 40 micrograms/mL eye drops, solution – SPC

17. Timoptol Unit Dose 0.25% and 0.5% w/v Eye Drops Solution – UK SmPC

18. Timolol eye drops 0.5% SPC

19. EMA – DuoTrav Scientific discussion
20. Module 2.4 Non clinical overview
21. Module 2.5 Clinical overview

22. Emilio Rintaro Suzuki Jr . Cibele Lima Belico Suzuki. Efficacy and safety of travoprost alone or in combination with other agents for glaucoma and ocular hypertension: patient considerations. Clinical Ophthalmology 2010:4 1165–1171

23. Cracknell KP, Grierson I. Prostaglandin analogues in the anterior eye: their pressure lowering action and side effects. Exp Eye Res. 2009 Apr;88(4):786-91.

24. Gábor Holló. The side effects of the prostaglandin Analogues Expert Opinion on Drug Safety, January 2007, Vol. 6, No. 1 : Pages 45-52

25. Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24

26. 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 , Pages S162-S175, August 2002

27. 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

28. 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

29. Ni Li MD, Xiao-ming Chen MD, Yong Zhou MD, Mao-ling Wei BA, Xun Yao MD. Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials. Clinical & Experimental Ophthalmology Volume 34, Issue 8, pages 755–764, November 2006

30. 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

31. G Holló - Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book)

32. Suominen S, Valimaki J. Bilateral anterior uveitis associated with travoprost. Acta Ophthalmol Scan 84(2): 275-6, 2006

33. Faulkner WJ, Burk SE. Acute anterior uveitis and corneal edema associated with travoprost. Arch Ophthalmol. 2003 Jul;121(7):1054-5.

34. Kumarasamy M & Desai SP (2004): Anterior uveitis is associated with travoprost. BMJ 329: 205.

35. Nikolas JS London, Sunir J Garg, Ramana S Moorthyand Emmett T Cunningham Jr. Drug-induced uveitis. London et al. Journal of Ophthalmic Inflammation and Infection 2013, 3:43

36. Weeranuj Yamreudeewong, PharmD, BCPS, CACP, Allison A. Dell, PharmD, Keri R. Pulley, FNP Patricia D. Stepp, MD. Asymptomatic Bradycardia Possibly Associated With Travoprost Therapy. Journal of Pharmacy Practice August 31, 2009

37. Alm A. Prostaglandin derivates as ocular hypotensive agents. Prog Retin Eye Res. 1998 Jul;17(3):291-312.

38. Mr Jeremy P. Diamond. Systemic Adverse Effects of Topical Ophthalmic Agents. Drugs & Aging. November 1997, Volume 11, Issue 5, pp 352-360

39. W H Frishman. Beta-adrenergic receptor blockers. Adverse effects and drug interactions. Hypertension. 1988;11:II21

40. Meuche C, Heidrich H, Bleckmann H. [Raynaud syndrome following timolol-containing eyedrops]. Fortschr Ophthalmol. 1990; 87(1):45-7.

41. 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

42. M. Detry-Morel. Side effects of glaucoma. Bull. Soc. belge Ophtalmol., 299, 27-40, 2006.

43. Marjo Volotinen, Expression of cytochrome P450-enzymes and metabolism of timolol in human ocular tissue, Academic dissertation

44. 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

45. 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.

46. Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: current literature and recommendations. Curr Opin Ophthalmol. 2013 Mar;24(2):136-43.

47. Herreras JM, Pastor JC, Calonge M, Asensio VM., Ocular surface alteration after long-term treatment with an antiglaucomatous drug. Ophthalmology. 1992 Jul; 99(7):1082-8.

48. 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.

49. M. Detry-Morel, Side effects of glaucoma medications Bull. Soc. belge Ophtalmol., 299, 27-40, 2006.

50. John H. Toogood. Beta-blocker therapy and the risk of anaphylaxis. CMAJ, VOL. 136, MAY 1, 1987

51. Dr David M. Lang. Anaphylactoid and Anaphylactic Reactions. Drug Safety, May 1995, Volume 12, Issue 5, pp 299-304

52. 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)

53. Timolol disease interactions—Drug information on line

54. 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

55. Chapter 54e. Glaucoma associated with retinal disorders and retinal surgery

56. 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.pt

57. Ohrström A, Kättström O. Interaction of timolol and adrenaline. Br J Ophthalmol 1981 Jan; 65(1):53-5.

58. 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.

59. Chapter 63: Anesthesia for Eye, Ear, Nose, and Throat Surgery

60. Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312-34.

61. Baudouin C. Allergic reaction to topical eyedrops. Curr Opin Allergy Clin Immunol. 2005 Oct;5(5):459-63.

62. Hong J, Bielory L. Allergy to ophthalmic preservatives. Curr Opin Allergy Clin Immunol. 2009 Oct;9(5):447-53.

63. Ocular Melanoma - Melanoma Research Foundation

64. Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book)

65. Albert Alm, Ian Grierson, M. Bruce Shields. Side Effects Associated with Prostaglandin Analog Therapy Survey of Ophthalmology Volume 53, Issue 6, Supplement, November 2008, Pages S93‑S105

66. Intraocular (Uveal) Melanoma Treatment - National Cancer Institute

67. CY Chung, AKH Kwok, KL Chung. Use of ophthalmic medications during Pregnancy. Hong Kong Med J Vol 10 No 3 June 2004

68. Barnebey HS, Orengo-Nania S, Flowers BE, Samples J, Mallick S, Landry TA, Bergamini MV. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol. 2005 Jul;140(1):1-7.

69. Franks WA, Renard JP, Cunliffe IA, Rojanapongpun P. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0:005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. Clin Ther. 2006 Mar;28(3):332-9.

70. K Inoue, M Shiokawa, R Higa, M Sugahara, T Soga, M Wakakura and G Tomita. Adverse periocular reactions to five types of prostaglandin analogs. Eye (2012) 26, 1465–1472

71. Hany A. Khairy, FRCSEd, FRCSG, MD, Khaled Said-Ahmed, FRCSG, MD. A Short-term Randomized Clinical Trial of Daily Versus Alternate Day Use of Travoprost 0.004% in the Treatment of Ocular Hypertension. J Glaucoma. 2013;22(2):123-126.

72. Jess T Whitson. Travoprost-a new prostaglandin analogue for the treatment of glaucoma. Expert Opth. Pharmather. (2002) 3 (7):965-977

73. Agorastos Agorastos and Christian G. HuberReview article. The role of melatonin in glaucoma: implications concerning pathophysiological relevance and therapeutic potential. J. Pineal Res. 2011; 50:1–7

74. Caprioli Jet al. Blood pressure, perfusion pressure, and glaucoma. Am J Ophthalmol. 2010 May;149(5):704-12

75. Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. JAMA. 1998 Aug 12;280(6):539-43.

76. Herng-Ching Lin, Ching-Wen Chien, Chao-Chien Hu, Jau-Der Ho, MD. Comparison of Comorbid Conditions between Open-Angle Glaucoma Patients and a Control Cohort : A Case-Control Study. Ophthalmology, volume 117, issue 11, November 2010, Pages 2088–2095

77. Ho JD, Hu CC, Lin HC.Open-angle glaucoma and the risk of stroke development: a 5-year population-based follow-up study. Stroke. 2009 Aug;40(8):2685-90.

78. Mitchell P, Lee AJ, Rochtchina E, Wang JJ.Open-angle glaucoma and systemic hypertension: the blue mountains eye study. J Glaucoma. 2004 Aug;13(4):319-26.

Abbreviations:

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