# *[TRAVOPROST] PRESERVATIVE-FREE 40 MICROGRAMS/ML EYE DROPS*

## RISK MANAGEMENT PLAN

TRAVOPF-v1-250915

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|---|---|
| Active substance(s) (INN or common name): | **Travoprost** |
| Pharmaco-therapeutic group (ATC Code): | **S01E E04** |
| Name of Marketing Authorisation Holder or Applicant: | **Pharmathen SA** |
| Number of medicinal products to which this RMP refers: | **1** |
| Product(s) concerned (brand name (s)): | Traglafka, 40 micrograms/ml (DK, UK, EL, ES, FR, DE) |

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| Data lock point for this RMP | 25.09.2015 | Version number | TRAVOPF-v1-250915 |
| Date of final sign off | 25.09.2015 | | |

# RISK MANAGEMENT PLAN

## PART I: PRODUCT(S) OVERVIEW

*[Travoprost] preservative-free 40µg/ml, 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 authorization 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 | | - | Not applicable |
| Part IV Plan for post-authorisation efficacy studies | | - | Not applicable |
| Part V Risk minimization Measures | | - | Not applicable |
| Part VI Summary of RMP | | - | Not applicable |
| Part VII | ANNEX 1 | - | Not applicable |

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| Annexes | Eudravigilance Interface | | |
| | ANNEX 2<br>Current or proposed SmPC/PIL | 09.2015 | v.01 |
| | ANNEX 3<br>Worldwide marketing status by country | - | v.01 |
| | ANNEX 4<br>Synopsis of on-going and completed clinical trial programme | - | v.01 |
| | ANNEX 5<br>Synopsis of pharmacoepidemiological study program | - | v.01 |
| | ANNEX 6<br>Protocols for proposed and on-going studies in Part III | - | v.01 |
| | ANNEX 7<br>Specific adverse event follow-up forms | - | v.01 |
| | ANNEX 8<br>Protocols for studies in Part IV | - | v.01 |
| | ANNEX 9<br>Synopsis of newly available study reports in Parts III-IV | - | v.01 |
| | ANNEX 10<br>Details of proposed additional risk minimization activities | - | v.01 |
| | ANNEX 11<br>Mock up examples | - | v.01 |
| | ANNEX 12<br>Other supporting data | Refer to pg. 89 | v.01 |

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|---|---|
| QPPV name | |
| 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 | TRAVOPF-v1-250915 |
| Agreed with | DK/H/2599/001/DC |

**Current RMP versions under evaluation:**

Not applicable.

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| **Invented name (s) in the European Economic Area (EEA)** | Traglafka, 40 micrograms/ml (DK, UK, EL, ES, FR, DE) |
| **Authorisation procedure** | DK/H/2599/001/DC |
| **Brief description of the product including:** | |
| • Chemical class | Travoprost is a prostaglandin $F_{2\alpha}$ analogue.<br>Pharmacotherapeutic group: Ophthalmologicals – antiglaucoma preparations and miotics – prostaglandin analogues |
| • Summary of mode of action | Travoprost, a prostaglandin F2a analogue, is a highly selective full agonist which 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 the intraocular pressure in man starts about 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. |
| • 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) | Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma |
| **Posology and route of administration in the EEA** | |
| Current (if applicable) | Not applicable. |
| Proposed (if applicable) | *Use in adults, including elderly population*<br>The dose is one drop of [PRODUCT NAME] Preservative-free in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the |

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| | evening.<br><br>Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.<br><br>If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart.<br><br>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.<br><br>When substituting another ophthalmic antiglaucoma medicinal product with [PRODUCT NAME] Preservative-free, the other medicinal product should be discontinued and [PRODUCT NAME] Preservative-free should be started the following day.<br><br>*Hepatic and renal impairment*<br>[PRODUCT NAME] Preservative-free 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 dosage adjustment is necessary in these patients.<br><br>*Paediatric population*<br>The efficacy and safety of [PRODUCT NAME] Preservative-free in children below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.<br><br><u>Method of Administration</u><br><br>For ocular use.<br>For patients who wear contact lenses please refer to section 4.4.<br><br>[PRODUCT NAME] preservative-free eye drops solution, multidose container is a sterile solution that does not contain a preservative. The solution from the multi-dose container is to be used for 28 days after opening for administration to the affected eye(s). Since sterility can be maintained after the multi- dose container is opened, the remaining content must not be discarded before the 28 days after opening. |

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| | Patients should be instructed to wash their hands before use and avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.<br><br>The patient should remove the protective overwrap (if there is one) immediately prior to initial use. After cap is removed, [PRODUCT NAME] preservative-free eye drops solution, multi-dose container is ready for use. 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. |
| **Pharmaceutical form (s) and strengths**<br><br>Current (if applicable) | Not applicable. |
| Proposed (if applicable) | 40µg/ml Eye drops solution.<br>Clear, colourless aqueous solution. |

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| 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

The present application of travoprost 40 micrograms/mL preservative free eye drops, solution in multi dose container complies with the definition of a "hybrid" medicinal product as stated in Article 10(3) of Directive 2001/83/EC as amended. The reference medicinal product is TRAVATAN® 40 micrograms/ml eye drops, solution, which has been authorized in the European community for more than ten years (first approved on 29-11-2001) by means of a centralized procedure. 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] preservative-free 40µg/mL, eye drops, solution'* is indicated for decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

***Brand names of concerned products (with this indication):***

Traglafka, 40 micrograms/ml

## SI.1 Epidemiology of the disease

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

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| **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.<br>OHT 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.<br>Over a 5-year period, several studies have shown the incidence of glaucomatous damage in people with OHT 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.<br>In approximately 3% of people with OHT, the veins in the retina can become blocked (called a retinal vein occlusion), which could lead to vision loss.<br>Some studies have found that the average intraocular |

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| | pressure in blacks is higher than in whites, while other studies have found no difference.<br>• A 4-year study showed that blacks with OHT 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.<br>• In addition, blacks are considered to have a 3-4 times greater risk of developing primary open-angle glaucoma (POAG). They are also believed to be more likely to have optic nerve damage.<br>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.<br>• Some studies suggest that women could be at a higher risk for OHT, especially after menopause.<br>• Studies also show that men with OHT 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. OHT has a 10-15 times greater prevalence than pseudoexfoliative glaucoma. |
| **Mortality in target indication** | OHT 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 OHT and 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**<br>Although black individuals are considered to have a 3-4 times higher prevalence of POAG and larger cup- |

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| | to-disc ratios compared with white individuals, the data are less clear concerning OHT. 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.<br>**2. Sex-related demographics**<br>The Barbados Eye Study found OHT present more frequently in women.<br>**3. Age-related demographics**<br>Mean intraocular pressure slowly rises with increasing age. Age older than 40 years is considered a risk factor for the development of OHT and POAG. |
| **References** | Anne Chang-Godinich, Ocular hypertension medications. http://emedicine.medscape.com<br><br>Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol*. Aug 1997;115(8):1051-7.<br><br>Chihara E. Assessment of true intraocular pressure: the gap between theory and practical data. *Surv Ophthalmol*. May-Jun 2008;53(3):203-18.<br><br>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.<br><br>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. |

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| **Indication/target population** | **Primary open angle glaucoma (POAG)** 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.<br>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.<br>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.<br>Studies over the last 20 years have helped to characterize those with OHT.<br>Recent data on people with OHT 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. OHT is 10-15 times more likely to occur than POAG, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will |

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| | 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. OHT 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** | OHT 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.<br>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 POAG 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.<br><br>***By age* group**, the highest proportion will continue to be contributed by those aged 70–79 years (31% in 2011 vs. 32% in 2050).<br><br>**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).<br><br>***By race and ethnicity***, the highest proportion of the |

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| | 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.<br><br>Murray F, American Optometric Association-OAG.<br><br>Jerald A Bell, MD, Ocular Hypertension http://www.emedicinehealth.com/ocular_hypertension<br><br>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.<br><br>Mukhtar Bizrah, Li Guo, Maria Francesca Cordeiro. Glaucoma and Alzheimer's Disease in the Elderly. Aging Health. 2011;7(5):719-733.<br><br>Anne Chang-Godinich, Ocular hypertension medications. http://emedicine.medscape.com<br><br>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. In addition, if the intraocular pressure is not adequately controlled with travoprost, additional agents such as intraocular beta-blockers (betaxolol, carteolol, levobunolol, metipranolol, timolol) will be employed.

## 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** | |
| **Acute Toxicity**<br>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. | Unrelated |
| **Chronic Toxicity**<br>Repeated-dose ocular studies in the rabbit, up to 6 months in duration, were uneventful apart from some minor changes in serum chemistry parameters. In the 6-month study, the NOAEL corresponded to ca 5 times the maximum intended clinical exposure. The plasma concentration of AL-5848 at 30 min after dosing was 8-18 times the clinical $C_{max}$. In a 12-month ocular study in the monkey, increased iris pigmentation and minor corneal epithelium surface irregularity were observed with both travoprost and the positive control latanoprost, and so appear to be class effects for PGF2α analogues. The slight, species-specific, enlarged-eye syndrome observed with travoprost at doses similar to those intended for clinical use has also been reported for other prostanoid receptor agonists.<br>Repeated-dose systemic toxicity studies up to 6 months' duration in rodents were uneventful in the mouse but revealed dose-related hyperostosis and endosteal fibrosis in femur and sternum, as well as splenic extramedullary haematopoiesis in the rat. The effects on bone appear to be pharmacologically mediated and are possibly specific to the rat. At the NOAEL for effects on bone, plasma AL-5848 concentration was virtually 100 times the anticipated clinical $C_{max}$. | Unrelated |
| **Carcinogenicity**<br>The carcinogenic potential of travoprost has been investigated in two-year studies in rats and mice. There was no evidence of carcinogenic potential at doses up to and including 100 µg/kg/day when administered by s.c. injection to rats or mice. | Unrelated |
| **Genotoxicity**<br>The standard battery of genotoxicity tests, three *in-vitro* and two *in-vivo* studies, showed no evidence of genotoxic potential. Bacterial reverse mutation assays in *S. typhimurium* and *E. coli* were negative. In one mouse lymphoma assay, there were somewhat equivocal results, but a repeat assay was negative. A mouse micronucleus assay and a rat bone marrow chromosome aberration assay, both gave negative results. | Unrelated |
| **Mutagenicity** | |

| Safety from non- clinical studies | Relevance to human usage |
|---|---|
| **Toxicity** | |
| Travoprost did not cause gene mutation in bacteria or chromosomal aberrations in bone marrow cells of mice and rats. A slight increase in mutation frequency was observed in one or two mouse lymphoma L5178Y assays. | Unrelated |
| **Reproduction & Development**<br>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). | The use of travoprost in women who are or may become pregnant should therefore be contraindicated. |
| **General safety pharmacology** | |
| Intra ocular pressure (IOP) reduction is efficiently achieved by the prostaglandins. Among them, travoprost can lower IOP levels to 6.5–9.0 mmHg, being as effective as products combining timolol with latanoprost or dorzolamide. Other benefits of travoprost include probable increased efficacy in black patients, eyes with pseudoexfoliation, eyes with chronic angle-closure glaucoma, and following cataract surgery. Even though the recommended dosing is once daily, travoprost can lower IOP up to 63 hours after the last dose, demonstrating greater IOP control at the end of each dose compared with latanoprost.<br>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 therapy, the efficiency and safety of travoprost have been extensively demonstrated. | Safety and efficacy profile of travoprost in humans is well established |
| **Mechanisms for drug interactions** | |
| The plasma protein binding of the active free acid form of travoprost is moderate (approximately 80%) and, therefore, drug-drug interactions involving protein binding are unlikely. | Unlikely |
| References of module SII | *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC |

| Safety from non- clinical studies | Relevance to human usage |
|---|---|
| **Toxicity** | |
| | Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010<br><br>FDA Travatan label 2011<br><br>EMA – Travatan Scientific discussion<br><br>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. |

## SII Conclusions on non-clinical data

Safety and efficacy profile of travoprost in humans is well established. Animal studies have not shown toxic, carcinogenic or mutagenic effect for 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). Thus, the use of Travoprost in women who are or may become pregnant should therefore be contraindicated.

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 therapy, the efficiency and safety of travoprost have been extensively demonstrated.

Therefore, no significant risk for human safety is expected with therapeutic doses of travoprost preservative free eye drops solution.

## Module SIII: Clinical trial exposure

### SIII.1 Brief overview of development

*'[Travoprost] preservative-free 40 micrograms/ml eye drops'* is a generic formulation of Travatan® eye drops, solution (Allergan). This is being a 'hybrid' application under the Article 10(3) of European Directive 2001/83/EC.

### SIII.2 Clinical Trial exposure

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

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

| **Special population** | |
|---|---|
| Patients with renal impairment | Travoprost has been studied in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). The results of this trial showed that travoprost 0.004% did not accumulate in patients with several degrees of impaired renal function.<br>Therefore, no dosage adjustment is necessary in these patients.<br>One study has been performed in patients with renal impairment (C-99-97) in order to assess the pharmacokinetic parameters in subjects with normal and impaired renal function. No efficacy parameters were measured in this trial. The results of this trial showed that travoprost 0.004% did not accumulate in patients with several degrees of impaired renal function.<br>There is thus no pharmacological reason to think that efficacy in patients with impaired renal function would be different from patients with normal renal function.<br>Therefore, no dosage adjustment is necessary in these patients. |
| Patients with hepatic impairment | Travoprost has been studied in patients with mild to severe hepatic impairment. The results of this trial showed that travoprost 0.004% did not accumulate in patients with several degrees of impaired hepatic function. Therefore, no dosage adjustment is necessary in these patients. |

## Module SIV: Populations not studied in clinical trials

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

| **Special Population** | |
|---|---|
| Women of child-bearing potential/contraception | Travoprost must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place.<br>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).<br>In addition, travoprost is biologically active material 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, the exposed area should be cleaned immediately. |
| Pregnancy | Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. Travoprost should not be used during pregnancy unless clearly necessary. |
| 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. The use of travoprost by breast-feeding mothers is not recommended. |
| Paediatric patients | The efficacy and safety of travoprost 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. |
| Travoprost use by patients with inflammatory ocular conditions | There is no experience of travoprost in inflammatory ocular conditions or 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.<br>Caution is recommended when using travoprost 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. |

## Module SV - Post-authorisation experience

Since there are no safety concerns regarding safety and efficacy of **'***[Travoprost] preservative-free 40µg/mL, 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] preservative-free 40µg/mL, eye drops, solution'* is a generic formulation of *'Travatan 40µg/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. Formulation of the product, eyes drops solution, is administered by healthcare professionals. Therefore the possibility for overdose is very limited. Eyes drop solution is also contained in a white multi dose ophthalmic container. 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 belongs to 'antiglaucoma preaparations and miotics' pharmacotherapeutic group (ATC code: S01E E04). Thus, if more than one topical ophthalmic medicinal product should be used, the medicinal products must be administered at least 5 minutes apart.

Carefully considering the safety of miotics is often most important for patients with heart conditions, as the drugs can increase heart rate as a side effect of relaxing the optic muscles. Headaches and mild nausea are also common.

Prostaglandins and prostaglandin analogues are biologically active materials 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, exposed area should be cleaned thoroughly immediately.

Travoprost, like all members of the prostaglandin class of intraocular pressure-lowering medications, is extremely well-tolerated systemically. In Phase III clinical trials with travoprost, no systemic side effects were noted to occur statistically more often in travoprost-treated subjects than in subjects treated with timolol or latanoprost. In addition, post-marketing surveillance has not revealed any unanticipated systemic adverse events associated with travoprost or other prostaglandin analogues.

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

All measures for eyes drop, solution proper use are described in the relative approved regulatory documentation.

## SVI.4 Potential for medication errors

Please note that there is limited potential for medication errors. The indications of the medicinal product are clearly mentioned in section 4.1 of the SPC and section 1 of PL.

*'[Travoprost] preservative-free 40µg/mL, 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. Adverse events occurred following systemic absorption, reported from post-marketing experience, without determined frequency, is: bradycardia, tachycardia, asthma aggravated, vertigo, tinnitus, PSA increased, hair growth abnormal. However, incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Therefore, there is no 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 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. Healthcare providers may also sometimes recommend the drug to treat other types of glaucoma but it is still indicated as an off-label use for this product since no extensive research data is available to prove its adequacy in treating these conditions.

However, there is no potential for serious harm if the product is administered 'off-label'.

## SVI.6 Specific paediatric issues

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

## SVI.7 Conclusions

There is no safety concerns related to this module.

## Module SVII: Identified and potential risks

Travoprost, a prostaglandin $F_{2a}$ analogue, is a highly selective full agonist which 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 the intraocular pressure in man starts about 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.

| **Important Identified Risk** | |
|---|---|
| **Macular oedema** | |
| Frequency with 95 % CI | Not known |
| Seriousness/outcomes | Macular edema occurs when fluid and protein deposits collect on or under the macula of the eye (a yellow central area of the retina) and causes it to thicken and swell (edema). The swelling may distort a person's central vision, as the macula is near the center of the retina at the back of the eyeball. This area holds tightly packed cones that provide sharp, clear central vision to enable a person to see detail, form, and color that is directly in the direction of gaze. |
| Severity and nature of risk | Possible adverse event. Vision loss may be mild to severe, but in many cases, peripheral (side) vision remains. |
| 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.<br>Arachidonic acid may promote the increase of eicosanoids as well as other proinflammatory mediators in the eye, ultimately leading to changes in the blood–aqueous and blood–retinal barriers. |
| Preventability | The edema resolves, and visual acuity returns, upon cessation of prostaglandin therapy. |
| Impact on individual patient | Deterioration of patient quality of life due to vision loss. |
| Potential public health impact of safety concern | Pseudophakic eyes and eyes with other risk factors for macular edema are most likely to be affected, and phakic eyes without risk factors may not be at risk. However, discontinuation of treatment in all populations (at risk or not) |

| **Important Identified Risk** | |
|---|---|
| **Macular oedema** | |
| | should be immediate. |
| Evidence source | *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010<br><br>Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24.<br><br>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.<br><br>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 | NA |

| **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 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 |

| **Important Identified Risk** | |
|---|---|
| **Hyperpigmentation** | |
| | 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] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010<br><br>Johan W Stjernschantz, MD, PhD, Daniel M Albert, MD, Dan-Ning Hu, MD, Filippo Drago, MD, PhD, Per J Wistrand, MD, PhD. Mechanism and Clinical Significance of Prostaglandin-Induced Iris Pigmentation. Survey of Ophthalmology Volume 47, Supplement 1, August 2002, Pages S162–S175.<br><br>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.<br><br>Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24.<br><br>Emilio Rintaro Suzuki Jr, Cibele Lima Belico Suzuki. |

| **Important Identified Risk** | |
|---|---|
| **Hyperpigmentation** | |
| | 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 | NA |

| **Important Identified Risk** | |
|---|---|
| **Hypertrichoses** | |
| Frequency with 95 % CI | Uncommon (>1/1,000 to <1/100) |
| 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 frequency of eyelashes changes vary 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 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 pshysicological effects on the patients. In the female patients, |

| **Important Identified Risk** | |
|---|---|
| **Hypertrichoses** | |
| | the stimulation of lash growth can have appositive phsychological 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] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010.<br><br>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.<br><br>Holló G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf. 2007 Jan;6(1):45-52.<br><br>G Holló - Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book). |
| MedDRA terms | NA |

| **Important Identified Risk** | |
|---|---|
| **Iris and uveal inflammation** | |
| Frequency with 95 % CI | Uncommon (>1/1,000 to <1/100) |
| Seriousness/outcomes | Iritis is inflammation that affects a part of your eye called the iris. The iris is the colored ring of tissue surrounding your pupil. Its part of the middle layer of the eye known as the uvea, which is why this condition is considered a type of uveitis, or inflammation of the uvea. Because the iris is located at the front of the uvea, iritis is sometimes called anterior uveitis. Iritis is a serious condition that, if left untreated, could lead to glaucoma or blindness. |
| 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 &* |

| **Important Identified Risk** | |
|---|---|
| **Iris and uveal inflammation** | |
| | Desai (2004)).<br>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] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010<br><br>Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24.<br><br>Suominen S, Valimaki J. Bilateral anterior uveitis associated with travoprost. Acta Ophthalmol Scan 84(2): 275-6, 2006.<br><br>Faulkner WJ, Burk SE. Acute anterior uveitis and corneal edema associated with travoprost. Arch Ophthalmol. 2003 Jul;121(7):1054-5.<br><br>Kumarasamy M & Desai SP (2004): Anterior uveitis is associated with travoprost. BMJ 329: 205.<br><br>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. |

| **Important Identified Risk** | |
|---|---|
| **Iris and uveal inflammation** | |
| MedDRA terms | NA |

| **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 drug. |
| Background incidence/prevalence | Can not be determined. Adverse event reported either from clinical trials or been reported during product use in clinical practice. |
| Risk groups or risk factors | Elderly and patients with cardiac, respiratory or neurological disease. |
| Potential mechanisms | Possibly by stimulation of prostaglandin F (FP) receptor outside the eye. |
| Preventability | In elderly and patients with cardiac, respiratory or neurological disease that may be induced or exacerbated by topical ophthalmic agents' use of travoprost 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] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010.<br><br>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.<br><br>Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical Ophthalmology 2007:1(1) 11–24.<br><br>Alm A. Prostaglandin derivates as ocular hypotensive agents. Prog Retin Eye Res. 1998 Jul;17(3):291-312. |

| **Important Identified Risk** | |
|---|---|
| **Cardiac and vascular disorders** | |
| | Mr Jeremy P. Diamond. Systemic Adverse Effects of Topical Ophthalmic Agents. Drugs & Aging. November 1997, Volume 11, Issue 5, pp 352-360. |
| MedDRA terms | NA |

| **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. |
| 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. |
| Background incidence/prevalence | Can not be determined. For latanoprost upper respiratory tract infection the rate was of approximately 4% in clinical trials. |
| Risk groups or risk factors | Topical applied prostaglandin analogues should be avoided in patients with severe corticodependent asthma. |
| 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. |
| Preventability | Patients with severe corticodependent asthma should be advised not to take this product. |
| Impact on individual patient | Potential adrevrse events: Dysponea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation. |
| Potential public health impact of safety concern | Prostaglandins related systemic adverse events occurring via nasopharyngeal mucosal absorption are infrequently seen due to a relatively rapid elimination half-life. |
| Evidence source | *'[Travoprost] preservative- free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010.<br><br>Philippe Denis, David Covert, Anthony Realini. Travoprost in the management of open-angle glaucoma and ocular |

| **Important Identified Risk** | |
|---|---|
| **Respiratory disorders** | |
| | hypertension. Clinical Ophthalmology 2007:1(1) 11–24.<br><br>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.<br><br>M. Detry-Morel. Side effects of glaucoma. Bull. Soc. belge Ophtalmol., 299, 27-40, 2006. |
| MedDRA terms | NA |

**Others risks related to the product**

| **Important Potential Risk** | |
|---|---|
| **Ocular and skin melanomas** | |
| Frequency with 95 % CI | Not known |
| Seriousness/outcomes | 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. |
| 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 |

| **Important Potential Risk** | |
|---|---|
| **Ocular and skin melanomas** | |
| | 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 life-threatening side effects. |
| Evidence source | *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010.<br><br>Ocular Melanoma - Melanoma Research Foundation.<br><br>Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book).<br><br>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.<br><br>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.<br><br>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 |

| **Important Potential Risk** | |
|---|---|
| **Use during pregnancy and lactation** | |
| | 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 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] preservative-free 40µg/mL, eye drops, solution'*- SmPC<br><br>*Travatan 40µg/mL, eye drops, solution'*- SmPC<br>Travatan FDA labeling<br><br>Pr Travatan Z – product Monograph. Alcon Canada Inc. Revised July 2010.<br><br>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

Interaction studies with other medicinal products and other forms of interation have not been performed with *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'*.

### SVII.4.2 Important identified and potential interactions

**Drug-Drug Interactions**

No concerns.

Since travoprost undergoes a biotransformation pathway similar to endogenous prostaglandin-$F_{2\alpha}$, and since systemic levels of active metabolite following topical ocular administration are negligible, interactions with concomitant medications in patients receiving topical ocular doses is unlikely. *In vitro* experiments have shown the travoprost free acid to be moderately bound (about 80%) to plasma proteins in humans, indicating drug-drug interactions through protein binding to be unlikely.

**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.

## Module SVIII: Summary of the safety concerns

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | • Macular oedema<br>• Hyperpigmentation<br>• Hypertrichoses<br>• Iris and uveal inflammation<br>• Cardiac and vascular disorders<br>• Respiratory disorders |
| **Important potential risks** | • Ocular and skin melanomas<br>• Use during pregnancy and lactation |
| **Missing information** | • Potential interactions |

# PART III: PHARMACOVIGILANCE PLAN

**Routine Pharmacovigilance Activities**

*'[Travoprost] preservative-free 40µg/mL, eye drops, solution'* is a generic formulation. Therefore, routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring. Process followed for *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'* under Article 10(3) of European Directive 2001/83/EC, includes collection and medical evaluation of Individual Case Safety Reports (ICSRs), expedited reporting of adverse drug reactions (ADRs), regular signal detection and signal evaluation, weekly screening of the scientific literature for ADR reports, maintenance and administration of the global safety database, preparation and processing of safety reports (e.g PSURs, etc), maintenance of the pharmacovigilance quality management system and standardised processes to define and decide on adequate measures for crisis management and risk minimization.

No additional Pharmacovigilance activities are established, based on the absence of safety concerns for *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'*.

## 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** |
| 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 |

| **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 |

## III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

### Action plans for safety concerns with additional pharmacovigilance requirements

No concerns. Since there are no indications that the safety of travoprost may vary over time or between different target population sub-groups, no additional risk minimization measures are required.

However, *'Travatan 40µg/mL, eye drops, solution'* (by Alcon Laboratories) PhV activities will be closely followed and evaluated during life cycle of the product. Therefore, if necessary 'Additional Pharmacovigilance Safety Activities' such as DHPCs, educational material for patients and physicians etc, as described in Module V of new GVP Guideline will apply (section III1 – III5).

## III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

No concerns

## III.4 Details of outstanding additional pharmacovigilance activities

No concerns

## III.5 Summary of the Pharmacovigilance Plan

No concerns

# PART IV: PLAN FOR POST-AUTHORISATION EFFICACY STUDIES

*'[Travoprost] preservative-free 40µg/mL, 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 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.

| **Macular oedema** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of macular oedema is already included in *sections 4.4 a*nd *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.4:***<br>*Aphakic patients*<br>*Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using travoprost 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.*<br><br>***Section 4.8:***<br>*Eye disorders*<br>*Not known: macular oedema, sunken eyes* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for |

| **Macular oedema** | |
|---|---|
| | announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Hyperpigmentation** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of hyperpigmentation is already included in *sections 4.4 a*nd *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.4:***<br>*Eye colour change*<br>*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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.*<br><br>*Periorbital and eye lid changes* |

| **Hyperpigmentation** | |
|---|---|
| | *In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also been observed with prostaglandin analogues.*<br><br>***Section 4.8:***<br>*Summary of the safety profile*<br>*In clinical trials with travoprost, the most common adverse reactions were ocular hypearemia and iris hyperpigmentation, occurring in approximately 20% and 6% of patients respectively.*<br><br>*Eye disorders*<br>*Common: iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation.* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |

| **Hyperpigmentation** | |
|---|---|
| Comment | Not applicable |

| **Hypertrichoses** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of hypertrchoses is already included in *sections 4.4 a*nd *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.4:***<br>*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.*<br><br>***Section 4.8:***<br>*Skin and subcutaneous tissue disorders:*<br>*Uncommon: skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis.* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality |

| **Hypertrichoses** | |
|---|---|
| | metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Iris and uveal inflammation** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of iris and uveal inflammation is already included in *sections 4.4 a*nd *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.4:***<br>*Iritis/uveitis*<br>*In patients with known predisposing risk factors for iritis/uveitis, travoprost should be used with caution.*<br><br>***Section 4.8:***<br>*Eye disorders*<br>*Uncommon: skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis.* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for |

| **Iris and uveal inflammation** | |
|---|---|
| | announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Cardiac and vascular disorders** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of cardiac and vascular disorders is already included in *section 4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.8:***<br>*Cardiac disorders*<br>*Uncommon: palpitations*<br>*Rare: heart rate irregular, heart rate decreased*<br>*Not known: chest pain, bradycardia, tachycardia.*<br><br>*Vascular disorders*<br>*Rare: blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care |

| **Cardiac and vascular disorders** | |
|---|---|
| | professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Respiratory disorders** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Warning on the increased risk of respiratory disorders is already included in *section 4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.8:***<br>*Respiratory, thoracic and mediastinal disorders*<br>*Uncommon: dyspnoea, asthma, nasal congestion, throat irritation*<br>*Rare: respiratory disorder, oropharyngeal pain, cough, dysphonia*<br>*Not known: asthma aggravated* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care |

| **Respiratory disorders** | |
|---|---|
| | professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Ocular and skin melanomas** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Prostaglandin analogues are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Warning on the increased risk is already included in *section 4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.8:***<br>*Eye disorders*<br>*Common: iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation*<br><br>*Skin and subcutaneous tissue disorders*<br>*Uncommon:skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case |

| **Ocular and skin melanomas** | |
|---|---|
| | assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **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 on the increased risk of travoprost use during pregnancy and lactation is already included in *sections 4.6* and *5.3* of the SmPC. In addition it is listed in *section 2* of the PL *(*risk communication to reduce the incidence of it).<br><br>***Section 4.6:***<br>*Women of child-bearing potential/contraception*<br>*Travoprost must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place.*<br><br>*Pregnancy*<br>*Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child.*<br>*[PRODUCT NAME] Preservative-free should not be used during pregnancy unless clearly necessary.* |

| | |
|---|---|
| **Use during pregnancy and lactation** | |
| | *Breastfeeding*<br>*It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of [PRODUCT NAME] Preservative-free by breast-feeding mothers is not recommended.*<br><br>*Fertility*<br>*There are no data on the effects of travoprost on human fertility. Animal studies showed no effect of travoprost on fertility at doses more than 250 times the maximum recommended human ocular dose.*<br><br>***Section 5.3***<br>*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 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).* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation |

| **Use during pregnancy and lactation** | |
|---|---|
| | • Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>Periodic assessments |
| Results of effectiveness measurement | Not applicable |
| Impact of risk minimisation | Not applicable |
| Comment | Not applicable |

| **Potential interactions** | |
|---|---|
| Objective(s) of the risk minimisation measures | Making aware of physicians and monitoring the risk |
| Routine risk minimisation measures | Information concerning limited data of travoprost potential interactions is already included in *section 4.5* of the SmPC.<br><br>***Section 4.5:***<br>*No interaction studies have been performed.* |
| | *Other routine risk minimisation measures:*<br>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 | • Scientific literature search performed in weekly basis for ADR reports. Targeted evaluation of each ADR on a case by case assessment for all active substances monitored<br>• Regular signal detection and signal evaluation<br>• Medical information (enquiries) database resulting from patients and health care professionals enquiries<br>• Weekly search of website of EMA, PRAC announcements, CMDh, Press releases for announced safety concerns |
| Criteria for judging the success of the proposed risk minimisation measures | Routine assessment of the overall performance of the Pharmacovigilance system using quality |

| **Potential interactions** | |
|---|---|
| | metrics. |
| Planned dates for assessment | Assessment takes place routinely through the ongoing pharmacovigilance activities.<br>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 and 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |
| Hyperpigmentation | SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Hypertrichoses | SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Iris and uveal inflammation | SmPC sections 4.4 and 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |
| Cardiac and vascular disorders | SmPC section 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |
| Respiratory disorders | SmPC section 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Ocular and skin melanomas | SmPC section 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Use during pregnancy and lactation | SmPC sections 4.6 and 5.3<br>PIL section 2<br>Prescription only medicine | None proposed |
| Potential interactions | SmPC section 4.5<br>Prescription only medicine | None proposed |

# 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<br>• Hyperpigmentation<br>• Hypertrichoses<br>• Iris and uveal inflammation<br>• Cardiac and vascular disorders<br>• Respiratory disorders |
| **Important potential risks** | • Ocular and skin melanomas<br>• Use during pregnancy and lactation |
| **Missing information** | • Potential interactions |

### VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

No concerns

### VI.1.3 Tables of post-authorisation efficacy studies

No concerns

### VI.1.4 Summary of risk minimisation measures

| **Safety concern** | **Routine risk minimization measures** | **Additional risk minimization measures** |
|---|---|---|
| Macular oedema | SmPC sections 4.4 and 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |
| Hyperpigmentation | SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Hypertrichoses | SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Iris and uveal inflammation | SmPC sections 4.4 and 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |
| Cardiac and vascular disorders | SmPC section 4.8<br>PIL section 4<br>Prescription only medicine | None proposed |

| | | |
|---|---|---|
| Respiratory disorders | SmPC section 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Ocular and skin melanomas | SmPC section 4.8<br>PIL sections 2 and 4<br>Prescription only medicine | None proposed |
| Use during pregnancy and lactation | SmPC sections 4.6 and 5.3<br>PIL section 2<br>Prescription only medicine | None proposed |
| Potential interactions | SmPC section 4.5<br>Prescription only medicine | None proposed |

## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

The term **ocular hypertension** usually refers to any situation in which the pressure inside the eye, called intraocular pressure, is higher than normal. Eye pressure is measured in millimeters of mercury (mm Hg). Normal eye pressure ranges from 10-21 mm Hg. Ocular hypertension is an eye pressure of greater than 21 mm Hg. Ocular hypertension should not be considered a disease by itself. Instead, ocular hypertension is a term that is used to describe individuals who should be observed more closely than the general population for the onset of glaucoma. 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. 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.

**Glaucoma** is a leading cause of irreversible blindness with 60 million cases worldwide and 2.2 million in the United States. Up to 50 percent of those with glaucoma are not aware they have it. Early diagnosis and treatment is critical to managing glaucoma. **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. Regular eye exams are essential to detect glaucoma and slow irreversible vision loss. If untreated, the disease can lead to blindness. In fact, 11.2 million people are predicted to go blind from glaucoma by the year 2020, due in part to lack of access to medical treatments and providers.

The worldwide prevalence of glaucoma is increasing. This is due in part to the rapidly aging population. Vision loss from glaucoma greatly impacts the independence of many people who are part of this aging population. In addition to the impact glaucoma has on personal lives, there is an increasing economic burden on society.

### VI.2.2 Summary of treatment benefits

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.

[Travoprost] preservative-free eye drops solution does not contain benzalkonium chloride, a preservative used to curb microbial activity. Exposure to preservatives is a major reason for the development of adverse effects as they have a potential to cause toxicity to the ocular surface, especially in the long-term therapies.

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.

### VI.2.3 Unknowns relating to treatment benefits

In the SmPC of *'[Travoprost] preservative-free 40µg/mL, 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**

| **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<br><br>*(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, | Yes, by discontinuation of the treatment and consultation of an ophthalmologist. |

| | | |
|---|---|---|
| | sewing or recognizing a face.<br>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. | |
| Change in the colour of iris (the coloured part of the eye)<br>*(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. | These changes are solely cosmetic in nature, and have not posed a health risk in any form. However, an ophthalmologist should be advised. |
| Increase of the length, thickness, colour and/or number of the eyelashes that may cause unusual hair growth on the eyelids<br><br>*(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. | These changes are solely cosmetic in nature. However, an ophthalmologist should be advised. |
| Pain, sensitivity to light, blurred vision, and redness<br><br>*(Iris and uveal inflammation)* | Uveitis and iritis are known adverse effects of travoprost (prostaglandin F2 analogues adverse event) and are most common with latanoprost.<br>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)<br><br>*(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 are adverse event related to systemic absorption of the drug that occurs rarely. However, topical applied travoprost | Yes, by discontinuation of the treatment and immediate consultation of a doctor. |

| | | |
|---|---|---|
| *(Respiratory disorders)* | should be avoided in patients with severe corticodependent asthma. | |

| **Important potential risks** | |
|---|---|
| **Risk** | **What is known (Including reason why it is considered a potential risk)** |
| Ocular and skin melanomas | Prostaglandin analogues are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Melanoma was not seen in the clinical trials for travoprost which studied 6,385 patients and healthy volunteers.<br>Three spontaneous cases of melanoma have been reported to date, two with travoprost and one with the fixed combination of travoprost and timolol.<br>Four cases have been reported in the literature with members of the same pharmaceutical class: one eyelid melanoma associated with bimatoprost (another type of prostaglandin analogue) and one choroidal melanoma and two cutaneous melanomas associated with latanoprost (another type of prostaglandin analogue). However, a direct link between prostaglandin analogue use and development of melanoma has never been documented. |
| Use during pregnancy and lactation | 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.<br><br>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).<br><br>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. |

| **Missing information** | |
|---|---|
| **Risk** | **What is known** |
| Potential interactions | Interaction studies with other medicinal products and other forms of interation have not been performed. |

### 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 | 25.09.2015 | **Important identified risks**<br>• Macular oedema<br>• Hyperpigmentation<br>• Hypertrichoses<br>• Iris and uveal inflammation<br>• Cardiac and vascular disorders<br>• Respiratory disorders<br>**Important potential risks**<br>• Ocular and skin melanomas<br>• Use during pregnancy and lactation<br>**Missing information**<br>• Potential interactions | Initial version |

# PART VII: ANNEXES

**Table of contents**

## *Annex 1 – EudraVigilance Interface*

Not applicable.

## 1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] Preservative-free 40 micrograms/mL eye drops solution, multi dose container

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 40 micrograms of travoprost.

Excipient(s) with known effect:
Each mL of solution contains 2 mg of macrogol glycerol hydroxyl stearate 40 (see section 4.4.)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma (see section 5.1).

### 4.2 Posology and method of administration

Posology
*Use in adults, including elderly population*
The dose is one drop of [PRODUCT NAME] Preservative-free in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

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).

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.

When substituting another ophthalmic antiglaucoma medicinal product with [PRODUCT NAME] Preservative-free, the other medicinal product should be discontinued and [PRODUCT NAME] Preservative-free should be started the following day.

*Hepatic and renal impairment*
[PRODUCT NAME] Preservative-free 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 dosage adjustment is necessary in these patients (see section 5.2).

*Paediatric population*
The efficacy and safety of [PRODUCT NAME] Preservative-free in children below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Method of Administration

For ocular use.
For patients who wear contact lenses, please refer to section 4.4.

[PRODUCT NAME] preservative-free eye drops solution, multidose container is a sterile solution that does not contain a preservative. The solution from the multi-dose container is to be used for 28 days after opening for administration to the affected eye(s). Since sterility can be maintained after the multi- dose container is opened, the remaining content must not be discarded before the 28 days after opening.

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

The patient should remove the protective overwrap (if there is one) immediately prior to initial use. After cap is removed, [PRODUCT NAME] preservative-free eye drops solution, multi-dose container is ready for use. 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.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Eye colour change
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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

Periorbital and eye lid changes
In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also 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 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. Travoprost should therefore be used with caution in patients with active intraocular inflammation.

Aphakic patients
Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using travoprost 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.

Iritis/uveitis
In patients with known predisposing risk factors for iritis/uveitis, travoprost should be used with caution.

Contact with the skin
Skin contact with travoprost must be avoided as transdermal absorption of travoprost has been demonstrated in rabbits.

Prostaglandins and prostaglandin analogues are biologically active materials 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.

Contact lenses
Patients must be instructed to remove contact lenses prior to application of [PRODUCT NAME] Preservative-free and wait 15 minutes after instillation of the dose before reinsertion.

Excipients
[PRODUCT NAME] Preservative-free contains macrogol glycerol hydroxyl stearate 40 which may cause skin reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

## 4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception
Travoprost must not be used in women of child bearing age/potential 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.
[PRODUCT NAME] Preservative-free should not be used during pregnancy unless clearly necessary.

Breastfeeding
It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of [PRODUCT NAME] Preservative-free by breast-feeding mothers is not recommended.

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

## 4.7 Effects on ability to drive and use machines

Travoprost has no or negligible influence on the ability to drive and use machines, however 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 machines.

## 4.8 Undesirable effects

Summary of the safety profile
In clinical trials with travoprost, the most common adverse reactions were ocular hypearemia and iris hyperpigmentation, occurring in approximately 2 0 % and 6 % of patients respectively.

Tabulated list of adverse reactions
The following adverse reactions are classified according to the following convention: very common (>1 /1 0 ), common (>1 / 1 0 0 to <1 /1 0 ), uncommon (>1 /1 , 0 0 0 to <1 /1 0 0 ), rare (>1 /1 0 , 0 0 0 to<1 /1 ,0 0 0 ), very rare <1 /1 0 ,0 0 0 ), or not known (frequency cannot be estimated from the available data). Within each frequency group, adverse reactions are

presented in decreasing order of seriousness. The adverse reactions were obtained from clinical studies and post marketing data with travoprost.

| System Organ Class | Frequency | Adverse Reactions |
|---|---|---|
| Infections and infestations | Rare | herpes simplex, keratitis herpetic |
| Immune system disorders | Uncommon | hypersensitivity, seasonal allergy |
| Psychiatric disorders | Not known | depression, anxiety |
| Nervous system disorder | Uncommon | headache, dizziness, visual field defect |
| | Rare | dysgeusia |
| Eye disorders | Very common | ocular hyperaemia |
| | Common | iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation |
| | Uncommon | corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of eyelid, periorbital oedema, eyelids pruritus, visual acuity reduced, vision blurred, lacrimation increased, conjunctivitis, ectropion cataract, eyelid margin crusting, growth of eyelashes, eyelash discolouration, asthenopia |
| | Rare | iridocyclitis, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, halo vision, conjunctival follicles, hypoaesthesia eye, meibomianitis, anterior chamber pigmentation, mydriasis, eyelash thickening |
| | Not known | macular oedema, sunken eyes |
| Ear and labyrinth disorders | Not known | vertigo, tinnitus |
| Cardiac disorders | Uncommon | palpitations |
| | Rare | heart rate irregular, heart rate decreased |
| | Not known | chest pain, bradycardia, tachycardia |
| Vascular disorders | Rare | blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension |
| Respiratory, thoracic and mediastinal disorders | Uncommon | dyspnoea, asthma, nasal congestion, throat irritation |
| | Rare | respiratory disorder, oropharyngeal pain, cough, dysphonia |
| | Not known | asthma aggravated |
| Gastrointestinal disorders | Rare | peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth |
| | Not known | diarrhoea, abdominal pain, nausea |
| Skin and subcutaneous | Uncommon | skin hyperpigmentation (periocular), skin |

| | | |
|---|---|---|
| tissue disorders | | discolouration,<br>hair texture abnormal, hypertrichosis |
| | Rare | dermatitis allergic, dermatitis contact, erythema, rash,<br>hair colour changes, madarosis |
| | Not known | pruritus, hair growth abnormal |
| Musculoskeletal and connective tissue disorders | Rare | musculoskeletal pain |
| | Not known | arthralgia |
| Renal and urinary disorders | Not known | dysuria, urinary incontinence |
| General disorders and administration site conditions | Rare | asthenia |
| Investigations | Not known | prostatic specific antigen increased |

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

No cases of overdose have been reported. A topical overdose is not likely to occur or to be associated with toxicity. A topical overdose of travoprost may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues
ATC code: S01E E04

Mechanism of action
Travoprost, a prostaglandin $F_{2a}$ analogue, is a highly selective full agonist which 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 the intraocular pressure in man starts about 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.

Clinical efficacy and safety
Data on adjunctive administration of travoprost with timolol 0.5% and limited data with

brimonidine 0.2% were collected during clinical trials that showed an additive effect of travoprost with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

## 5.2 Pharmacokinetic properties

Absorption
Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. Studies in rabbits have shown peak concentrations of 20 ng/g of the free acid in aqueous humour one to two hours after topical dosing of travoprost. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution
Following topical ocular administration of travoprost to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25 pg/ml or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit before 1 hour post-administration. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of active free acid in man could not be determined.

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 $F_{2a}$ 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.

Elimination
Travoprost free acid and its metabolites are mainly excreted by the kidneys. 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 dosage adjustment is necessary in these patients.

## 5.3 Preclinical safety data

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).

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Macrogolglycerol hydroxystearate 40
Boric acid
Mannitol
Sodium chloride
Propylene glycol
Sodium hydroxide (for pH-adjustment)
Purified water

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

1 year

After first opening, this medicine does not require any special storage conditions.

Before opening, keep bottle in overwrap pouch (if available) in order to protect from moisture.

[PRODUCT NAME] Preservative-Free eye drops solution, multi-dose container
should be used no longer than 28 days after first opening of the multi – dose container.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

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

[PRODUCT NAME] Preservative-free eye drops solution, multi-dose container is available in the following packaging configurations:
1 x 2.5 ml (single 2.5-ml multi dose container)
3 x 2.5 ml (three 2.5-ml multi dose containers)
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

## 8. MARKETING AUTHORISATION NUMBERS

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10 DATE OF REVISION OF THE TEXT

**Package leaflet: Information for the user**

**[Product Name] Preservative free 40 micrograms/ml eye drops solution, multi - dose container**

Travoprost

**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 [Product Name] Preservative Free is and what it is used for

[Product Name] Preservative Free eye drops are used to treat high pressure in the eye. This pressure can lead to an illness called **glaucoma**.

**High pressure in the eye.** Your eyeballs contain a clear, watery liquid which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the eye fills up faster than it empties, the pressure inside the eye builds up. If it gets too high, it can damage your sight.

[Product Name] Preservative Free is one of a group of medicines for glaucoma called prostaglandin analogues. It works by increasing the outflow of liquid, which lowers the pressure in the eye. It may be used on its own or with other drops e.g. beta-blockers, which also reduce pressure.

## 2. What you need to know before you use [Product Name] Preservative Free

### Do not use [Product Name] Preservative Free

- if you are allergic to travoprost or any of the other ingredients of this medicine (listed in section 6).

### Warnings and precautions

- **If you are under 18.** [Product Name] Preservative Free is not to be used by people under 18 years of age.

[Product Name] Preservative Free may:

- increase the length, thickness, colour and/or number of your eyelashes and may cause unusual hair growth on your eyelids.
- change the colour of your iris (the coloured part of your eye). This change may be permanent.
- rarely cause breathlessness or wheezing or increase the symptoms of asthma. **If you are concerned about changes in your breathing pattern when using this medicine talk to your doctor as soon as possible.**
- 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 product comes into contact with the skin then it should be washed off straight away.

### Children and adolescents

[Product Name] Preservative Free is not to be used by people under 18 years of age.

### Other medicines and [Product Name] Preservative Free

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

### Pregnancy and breast-feeding

**Do not use [Product Name] Preservative Free if you are pregnant.** If you think that you may be pregnant speak with your doctor right away. If you could become pregnant you must use adequate contraception whilst you use this medicine.

**Do not use [Product Name] Preservative Free if you are breast feeding.** This medicine may pass into your milk.

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 any medicine.

### Driving and using machines

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

### [Product Name] Preservative Free contains macrogol glycerol hydroxy stearate 40

This medicine contains macrogol glycerol hydroxy stearate 40, which may cause skin reactions.

## 3. How to use [Product Name] Preservative Free

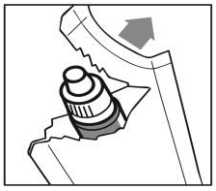
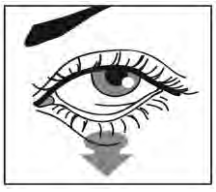
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Only use [Product Name] Preservative Free for dropping in your eyes.

### The recommended dose

Adults: **1 drop in the eye or eyes, once a day** – in the evening. Only use [Product Name] Preservative Free in both eyes if your doctor told you to. Use this medicine for as long as your doctor told you to.

### Instructions for use

| | |
|---|---|
|  **1a**  **1b** | 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 label in the space provided.<br>Get the medicine bottle and a mirror<br>Wash your hands.<br>Remove the cap. |
|  **2** | Hold the bottle, with the tip pointing down, between your thumb and fingers and press down on the bottom side **(picture 3)**.<br>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 2)**.<br>Bring the bottle tip close to the eye. Use the mirror if it helps. |

| | |
|---|---|
|  **3** | **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops.<br>Gently press down on the bottom side of the bottle to release one drop of medicine at a time **(picture 3)**.<br>After using the medicine, press a finger into the corner of your eye, by the nose **(picture 4)**. This helps to stop the medicine getting into the rest of the body. |
|  **4** | If you use drops in both eyes, repeat these same steps for your other eye.<br>Close the multi-dose container cap firmly immediately after use.<br>Only use one bottle of medicine at a time. Do not open the cap until you need to use the multi-dose container.<br>**You must throw away the bottle 4 weeks after you first opened it,** to prevent infections, and use a new bottle. |

**If a drop misses your eye,** try again.

**If you use more [Product Name] Preservative Free than you should**

Rinse all medicine out of your eye with warm water. Do not put in any more drops until it is time for your next regular dose.

**If you forget to use [Product Name] Preservative Free**

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 drop in the affected eye(s) daily.

**If you stop using [Product Name] Preservative Free**

Do not stop using this medicine without speaking to your doctor. This is because 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 [Product Name] Preservative Free and the other drops.

**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.

If you experience side effects, you can usually carry on taking the drops, unless the effects are serious. If you are worried, talk to your doctor or pharmacist. Do not stop taking [Product Name] Preservative Free without speaking to your doctor.

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

- Redness of the eye,
- Changes in the colour of the iris (coloured part of the eye).

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

Effects in the eye:

- inflammation inside the eye
- eye pain or swelling
- eye irritation
- eye discharge
- sensitivity to light
- blurred, reduced or abnormal vision
- dry eye
- itchy eye
- increased tear production
- abnormal or decreased eye sensation
- eyelid abnormality, irritation, itching, redness, pain, swelling or crusting
- discolouration of the eyelashes
- increased or decreased growth or number of eyelashes

Effects in the body:

- headache
- skin darkening around the eyes.

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

Effects in the eye:

- inflammation or infection of the conjunctiva (thin membrane that covers the inner surface of the eyelid and the white part of the eyeball) or cornea
- halo vision
- corneal disorder
- eye allergy
- tired eyes
- increase in pupil size

Effects in the body:

- asthma
- shortness of breath
- increased or decreased blood pressure

- irregular, increased, or decreased heart rate
- dizziness
- viral infection
- cough
- generalised weakness
- increased allergic symptoms
- throat irritation
- stuffy nose
- voice changes
- gastrointestinal discomfort or ulcer
- dry mouth
- constipation
- skin inflammation, redness or itching
- shoulder pain
- bad taste

**Additional side effects that have been reported include:**

Effects in the eye:

- inflammation of the back of the eye, sunken eyes.

Effects in the body:

- worsening of asthma
- ringing in ears
- increased prostate antigen (a protein produced by the prostate gland).

**Reporting of side effects**

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

## 5. How to store [Product Name] Preservative Free

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

Do not use this medicine after the expiry date which is stated on the bottle and the box after 'Exp'. The expiry date refers to the last day of the month.

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

Before opening, keep bottle in overwrap pouch (if available) in order to protect from moisture.

After first opening, this medicine does not require any special storage conditions.

**You must throw away the bottle 4 weeks after you first opened it,** to prevent infections. Write down the date you opened the bottle in the space on each 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 [Product Name] Preservative Free contains

- The active substance is travoprost. This medicine contains 40 micrograms/ml of travoprost.
- The other ingredients are macrogol glycerol hydroxy stearate 40, sodium chloride, propylene glycol, boric acid, mannitol, sodium hydroxide for pH adjustment and water for injection.

### What Product Name looks like and the contents of the pack

[Product Name] Preservative Free 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 [X] number of bottles.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

<to be completed nationally>

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<to be completed nationally>

**This leaflet was last revised in MM/YYYY.**

## *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)*

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**Abbreviations:**

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