[LATANOPROST] 50 MCG/ML PRESERVATIVE FREE EYE DROPS, SOLUTION

RISK MANAGEMENT PLAN

LATANO-v1-260417

TABLE OF CONTENTS

Active substance(s) (INN or common name):	**Latanoprost**
Pharmaco-therapeutic group (ATC Code):	**S01EE01**
Name of Marketing Authorisation Holder or Applicant:	**Pharmathen S.A**
Number of medicinal products to which this RMP refers:	**4**
Product(s) concerned (brand name (s)): Procedure: **DK/H/2755/001/DC** **DK, CY, FR, DE, GR, IT, ES**	**Tanafra** (DK, CY, GR, IT) **Tanafra 50 microgrammes/ml, collyre en solution** (FR) **Tanafra 50 Mikrogramm/ml Augentropfen, Lösung** (DE) **Tanafra 50 microgramos/ml colirio en solución** (ES)

Data lock point for this RMP 26.04.2017 Version number LATANO-v1-260417

Date of final sign off 28.04.2017

Active substance(s) (INN or common name):	**Latanoprost**
Pharmaco-therapeutic group (ATC Code):	**S01EE01**
Name of Marketing Authorisation Holder or Applicant:	**PharmaSwiss Česká republika s.r.o.**
Number of medicinal products to which this RMP refers:	**7**
Product(s) concerned (brand name (s)): Procedure: **DK/H/2754/001/DC** **DK, BG, CZ, GR, FR, HR, HU, NL, PL, SK**	**Vizilatan** (DK, CZ, HR, PL) **Визилат 0,05 mg/ml капки за очи, разтвор**T **anafra 50 Mikrogramm/ml** (BG) **Vizilatan 0,05 mg/ml, collyre en solution** (FR) **Visiolatan (**GR**)** **Vizilatan 0,05 mg/ml oldatos szemcsepp** (HU) **Vizilatan 0,05 mg/ml oogdruppels, oplossing** (NL) **Vizilatan 0,05 mg/ml** (SK)

Data lock point for this RMP	26.04.2017	Version number	LATANO-v1-260417
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RISK MANAGEMENT PLAN

PART I: PRODUCT(S) OVERVIEW

[LATANOPROST] 50 mcg/ml preservative free eye drops, solution
Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted /or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	-	Not applicable
	SII Non-clinical part of the safety specification	-	Not applicable
	SIII Clinical trial exposure	-	Not applicable
	SIV Populations not studied in clinical trials	-	Not applicable
	SV Post 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

Annexes	Eudravigilance Interface		
	ANNEX 2 Current or proposed SmPC/PIL	04.2017	Not applicable
	ANNEX 3 Worldwide marketing status by c ountry	-	Not applicable
	ANNEX 4 Synopsis of on-going and comple ted clinical trial programme	-	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiolo gical study program	-	Not applicable
	ANNEX 6 Protocols for proposed and on-go ing studies in Part III	-	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	-	Not applicable
	ANNEX 8 Protocols for studies in Part IV	-	Not applicable
	ANNEX 9 Synopsis of newly available stud y reports in Parts III-IV	-	Not applicable
	ANNEX 10 Details of proposed additional ris k minimization activities	-	Not applicable
	ANNEX 11 Mock up examples	-	Not applicable
	ANNEX 12 Other supporting data	Refer to pg. 85	Not applicable

MAH Name	Pharmathen S.A
QPPV name	
QPPV signature	
Contact person for this RMP	
E-mail address or telephone number of contact person	

MAH name	PharmaSwiss Česká republika s.r.o.
Deputy QPPV name	
Deputy QPPV signature	
Contact person for this RMP	
E-mail address or telephone number of contact person	

Overview of versions:

Version number of last agreed RMP:	-
Version number	LATANO-v1-260417
Agreed with	DK/H/2755/001/DC DK/H/2754/001/DC

Current RMP versions under evaluation:

Not applicable.

Invented name (s) in the European Economic Area (EEA)	[LATANOPROST] 50 mcg/ml preservative free eye drops, solution Tanafra (DK, CY, GR, IT) Tanafra 50 microgrammes/ml, collyre en solution (FR) Tanafra 50 Mikrogramm/ml Augentropfen, Lösung (DE) Tanafra 50 microgramos/ml colirio en solución (ES) Vizilatan (DK, CZ, HR, PL) Визилат 0,05 mg/ml капки за очи, разтворTanafra 50 Mikro gramm/ml (BG) Vizilatan 0,05 mg/ml, collyre en solution (FR) Visiolatan (GR) Vizilatan 0,05 mg/ml oldatos szemcsepp (HU) Vizilatan 0,05 mg/ml oogdruppels, oplossing (NL) Vizilatan 0,05 mg/ml (SK)
Authorisation procedure	DK/H/2755/001/DC DK/H/2754/001/DC
Brief description of the product including:	
• Chemical class	Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues
• Summary of mode of action	The active substance latanoprost, a prostaglandin F2α analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration of [Invented name] and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.
• Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	NA

Indication (s) in the EEA Current (if applicable)	NA
Proposed (if applicable)	Reduction of elevated intraocular pressure in patients with op en angle glaucoma and ocular hypertension. Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.
Posology and route of administration in the EEA Current (if applicable)	*NA*
Proposed (if applicable)	Recommended dosage for adults (including the elderly): The dosage of [Invented name] should not exceed once daily since it has been shown that more frequent administration de creases the intraocular pressure lowering effect. If one dose is missed, treatment should continue with the nex t dose as normal. As with any eye drops, to reduce possible systemic absorptio n, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This s hould be performed immediately following the instillation of each drop. Paediatric population: [Invented name] eye drops may be used in paediatric patients at the same posology as in adults. No data are available for pr eterm infants (less than 36 weeks gestational age). Data in th e age group < 1 year (4 patients) are very limited.
Pharmaceutical form (s) and strengths Current (if applicable)	NA

Proposed (if applicable)	
	Eye drops, solution. Clear, colorless, aqueous solution, free from visible particles. [LATANOPROST] 50 mcg/ml preservative free eye drops, so lution: Each mL of solution contains 50 micrograms of latano prost. Excipient with known effect Each mL of solution contains mg Macrogolglycerol hydroxystearate 40

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

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

PART II: SAFETY SPECIFICATION

[LATANOPROST] 50 mcg/ml preservative free eye drops, solution' is a generic formulation of *XALATAN ® 0,005 % m/V; collyre en solution* (Pfizer). This is being a 'hybrid' application under Article 10(3) of European Directive 2001/83/EC.
Therefore, all Modules of Part II (from module SI to Module SVIII) are applicable.

Module SI: Epidemiology of the indication(s) and target population(s):

Indication:

[LATANOPROST] 50 mcg/ml preservative free eye drops, solution is indicated for thereduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension and the reduction of elevated intraocular pressure in pediatric patients with elevated intraocular pressure and pediatric glaucoma sufferers.

Brand names of concerned products (with this indication):
DK/H/2755/001/DC:

- Tanafra *(DK, CY, GR, IT)*
- Tanafra 50 microgrammes/ml, collyre en solution (FR)
- Tanafra 50 Mikrogramm/ml Augentropfen, Lösung (DE)
- Tanafra 50 microgramos/ml colirio en solución (ES)

DK/H/2754/001/DC:

- Vizilatan (DK, CZ, HR, PL)
- Визилат 0,05 mg/ml капки за очи, разтворTanafra 50 Mikrogramm/ml (BG)
- Vizilatan 0,05 mg/ml, collyre en solution (FR)
- Visiolatan (GR)
- Vizilatan 0,05 mg/ml oldatos szemcsepp (HU)
- Vizilatan 0,05 mg/ml oogdruppels, oplossing (NL)
- Vizilatan 0,05 mg/ml (SK)

SI.1 Epidemiology of the disease

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

Indication/target population	**Ocular hypertension** Ocular hypertension (OHT) 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.
Incidence of target indication	According to the American Academy of Ophthalmology

	(AAO), the rate at which patients with elevated IntraOcular Pressure (IOP) develop glaucomatous optic nerve damage is approximately 1 percent per year, which is over 40,000 patients per year. This precursor condition is a prime contributor to the glaucoma patient pool.
Prevalence of target indication	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 IOPs of 21 mm Hg or higher without detectable signs of glaucomatous damage. Ocular hypertension has a 10-15 times greater prevalence than Primary Open Angle Glaucoma (POAG).
Mortality in target population	With regard to ocular morbidity and mortality, retinal vascular occlusion may occur in approximately 3% of ocular hypertensive patients. Progression to glaucoma is the main source of ocular morbidity and mortality. Studies have shown that over a 5-year-period, the incidence of glaucomatous damage in ocular hypertensive patients increases with increasing IOP levels: • IOP of 21-25 mm Hg - Approximately 2.6-3% • IOP of 26-30 mm Hg - Range from 12-26% • IOP higher than 30 mm Hg - Approximately 42% The Ocular Hypertension Treatment Study (OHTS) states that over a 5-year-period, patients with ocular hypertension 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.
Potential health risk	Prospective studies in the 1980s showed that among patients with elevated IOP, roughly 0.5-1% per year developed glaucoma over a period of 5-10 years. The OHTS suggests that progression to glaucoma increases with higher IOPs and lower central corneal thickness (CCT) and that certain patient characteristics are associated with a greater than 2% annual risk of developing glaucoma. Patient characteristics associated with this increased risk include the following: • Central corneal thickness of less than 555 μm - Annual risk of 3.4% • Vertical cup-to-disk ratio of greater than 0.30 - Annual risk of 2.5% • African American race - Annual risk of greater than 2%

Demographic profile of target population	*Race-related demographics* Although black individuals are considered to have a 3-4 times higher prevalence of POAG and larger cup-to-disc ratios compared with white individuals, the data are less clear concerning ocular hypertension. The Barbados Eye Study found the incidence of 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 IOP 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. *Sex-related demographics* The Barbados Eye Study found ocular hypertension present more frequently in women *Age-related demographics* Mean IOP slowly rises with increasing age. Age older than 40 years is considered a risk factor for the development of ocular hypertension and POAG.
References	Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol*. Aug 1997; 115(8):1051-7. Chihara E. Assessment of true intraocular pressure: the gap between theory and practical data. *Surv Ophthalmol*. May-Jun 2008; 53(3):203-18. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol. Aug 1991; 109(8):1090-5. Varma R, Wang D, Wu C, et al. Four-year incidence of open-angle glaucoma and ocular hypertension: the los angeles latino eye study. Am J Ophthalmol. Aug 2012; 154(2):315-325. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. Jun 2002; 120(6):714-20; discussion 829-30. Colton T, Ederer F. The distribution of intraocular pressures in the general population. Surv Ophthalmol.

	Nov-Dec 1980; 25(3):123-9. Higginbotham EJ, Gordon MO, Beiser JA, et al. The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals. Arch Ophthalmol. Jun 2004; 122(6):813-20. Hoehn R, Mirshahi A, Hoffmann EM, Kottler UB, Wild PS, Laubert-Reh D, et al. Distribution of intraocular pressure and its association with ocular features and cardiovascular risk factors: the Gutenberg Health Study. Ophthalmology. May 2013; 120(5):961-8. Luntz MH, Schenker HI. Retinal vascular accidents in glaucoma and ocular hypertension. Surv Ophthalmol. Nov-Dec 1980; 25(3):163-7. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol. Apr 2004;122(4):532-8 Medscape-Ocular hypertension

Indication/target population	**Primary open angle glaucoma (POAG)** Primary open-angle glaucoma is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an anterior chamber angle that is open by gonioscopic appearance.
Incidence of target population	Estimates vary as to the conversion rate from OHT to POAG, depending on subject selection and diagnostic criteria. It is likely that approximately 10% of individuals with persistent OHT will convert to POAG over a ten-year period. Risk factors for the conversion of OHT to POAG can be divided into ocular and systemic. Over a 5-year period, several studies have shown the incidence of glaucomatous damage in people with ocular hypertension to be about 2.6-3% for intraocular pressures of 21-25 mm Hg, 12-26% for intraocular pressures of 26-30 mm Hg, and approximately 42% for those higher than

	30 mm Hg. In approximately 3% of people with ocular hypertension, the veins in the retina can become blocked (called a retinal vein occlusion), which could lead to vision loss.
Prevalence of target population	Studies estimate that 3-6 million people in the United States alone, including 4-10% of the population older than 40 years, have intraocular pressures of 21 mm Hg or higher, without detectable signs of glaucomatous damage using current tests. Studies over the last 20 years have helped to characterize those with ocular hypertension. Recent data on people with ocular hypertension from the Ocular Hypertension Treatment Study have shown that they have an average estimated risk of 10% of developing glaucoma over 5 years. This risk may be decreased to 5% (a 50% decrease in risk) if eye pressure is lowered by medications or laser surgery. However, the risk may become even less than 1% per year because of significantly improved techniques for detecting glaucomatous damage. Patients with thin corneas may be at a higher risk for glaucoma development. Ocular hypertension is 10-15 times more likely to occur than primary open-angle glaucoma, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will have pressures higher than 21 mm Hg, but only 1 of those people will have glaucoma.
Mortality in target indication	Population-based cohort study of 4092 black participants (aged 40-84 years at baseline) in the Barbados Eye Studies. Open-angle glaucoma was defined by visual field defects and optic disc damage, based on standardized examinations and photograph gradings. Ocular hypertension was defined by an intraocular pressure greater than 21 mm Hg or treatment, without OAG damage. Mortality was ascertained from death certificates. Cox proportional hazards regression analyses determined associations with mortality. In this black population, cardiovascular mortality tended to increase in persons with previously diagnosed/treated OAG and ocular hypertension.
Potential health risk	Ocular hypertension cannot be prevented, but through regular eye examinations with an ophthalmologist, its progression to glaucoma can be prevented. Glaucoma is the second largest cause of blindness worldwide, estimated to affect 60.5 million people. It is also the leading cause of irreversible visual loss. By 2020, the

	number of glaucoma sufferers is estimated to increase to approximately 80 million. In the USA, for example, a 50% increase in the prevalence of glaucoma is expected by 2020. Risk factors for open-angle glaucoma include increased age, African ethnicity, family history, increased intraocular pressure, myopia, and decreased corneal thickness.
Demographic profile of target population	**Race-related demographics** Primary open-angle glaucoma (POAG) is the most prevalent form of glaucoma and has a particularly devastating impact in blacks. Blacks in many areas of the world are disproportionately affected by POAG. Large population-based studies such as the Barbados Eye Study showed that 1 in 11 Afro-Caribbean's over the age of 50 years, and 1 in 6 over the age of 70 years had open-angle glaucoma. Another population-based study was conducted in St. Lucia (West Indies), an island composed of a relatively homogeneous black population. Higher prevalence estimates of POAG in blacks 30 years of age and older were reported in St. Lucia, compared to the prevalence estimates reported for whites in other population-based studies. Similarly, population-based surveys conducted in African countries have shown the devastating impact of POAG in blacks. **Sex-related demographics** Reports on the prevalence of primary open-angle glaucoma between men and women differ. Although some studies have reported a significantly higher average intraocular pressure in women than in men (e.g. due to their shallower anterior chambers), other studies have not shown any difference between men. Other studies have even shown males to have a higher prevalence of glaucoma than women (e.g. The Rotterdam study). **Age-related demographics** Mean IOP slowly rises with increasing age. Age older than 40 years is considered a risk factor for the development of ocular hypertension and POAG.
References	Annette Giangiacomo, Anne Louise Coleman, The Epidemiology of Glaucoma Chapter 2 Murray F, American Optometric Association-OAG

Jerald A Bell, MD, Ocular Hypertension
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Wu SY, Nemesure B, Hennis A, Schachat AP, Hyman L, Leske MC; Barbados Eye Studies Group. Open-angle glaucoma and mortality: The Barbados Eye Studies. Arch Ophthalmol. 2008 Mar; 126(3):365-70. doi: 10.1001/archophthalmol.2007.77

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

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

Lyne Racette, M. Roy Wilson, Linda M. Zangwill, Robert N. Weinreb, and Pamela A. Sample. Primary Open-Angle Glaucoma in Blacks: A Review. Survey of ophthalmology Volume 48 • Number 3 • May–June 2003

Ida Dielemans, Johannes R. Vingerling, Roger C.W. Wolfs, Albert Hofman, Diederick E. Grobbee, Paulus T.V.M. de Jong .The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam study. Ophthalmology 1994; 101:1851-1855

David A Infeld, John G O'Shea Glaucoma: diagnosis and management. Postgrad Med. vol 7 1998;74:709-715

Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, Leske MC, Mitchell P, Congdon N, Kempen J, Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol. 2004; 122(4):532.

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020.
Br J Ophthalmol. 2006; 90(3):262.

Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC, Martone JF, Royall RM, Witt KA, Ezrine S. Racial differences in the cause-specific prevalence of blindness in east Baltimore N Engl J Med.

	1991;325(20):1412.

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 latanoprost, 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

Ocular hypertension

Potential comorbidities of Glaucoma including hypertension, heart failure, hyperlipidemia, diabetes, airways disease and depression (The Gutenberg Health Study)

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 signalling 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 prevalence 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 Ophtha

lmology also shows that having high blood pressure, it can also lead to glaucoma. In addition, inh aled steroids have been associated with the development of cataracts and while again these are mu ch more likely to occur in patients on frequent or maintenance oral corticosteroids, they are freque nt in patients attending severe asthma clinics. A meta analysis demonstrated an increased risk of 2 5% for each 1,000µg per day increase in the dose of beclomethasone equivalent inhaled steroid do se. 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 The adverse events profile of latanoprost is well characterised.The available published data on the preclinical safety of latanoprost are overall sufficient to assess the toxicological profile of the drug under discussion.	Unrelated
Single dose toxicity The oral and intravenous single dose toxicity of latanoprost was studied in mice and rats. Due to the low solubility in water, the maximum concentration of latanoprost in physiological saline was 40 µg/mL and the maximum injected dose was 2 mg/kg BW, approximately 50,000 times the human clinical dose. No mortality was observed. For oral single dose toxicity a solution of latanoprost in oil was used to achieve a higher concentration. The highest dose employed, i.e. 50 mg/kg BW (approximately 1 million times the clinical dose), did not induce any toxic symptoms. In a toxicity study in dogs, no mortality occurred at i.v. doses of 170, 340 or 680 µg/kg BW. In anaesthetised monkeys, intravenous administration of a single dose of 0.6 µg latanoprost per kg BW (approximately 10 times the human therapeutic dose) had no significant effect on arterial blood pressure, cardiac output, heart rate, cardiac work; no effects were noted with respect to the coronary blood flow. In addition, no changes of blood flow were observed in various parts of the brain, eye, gastrointestinal tract, liver, kidneys or bronchial arteries. High doses of latanoprost (6 µg/kg BW) administered intravenously to unanaesthetised monkeys approximately doubled the respiration rate probably reflecting bronchoconstriction of short duration; however, the animals showed no signs of	Unrelated

Safety from non- clinical studies	Relevance to human usage
dyspnoea. Minor changes in the ECG waveform were also recorded.	
Genotoxicity The *in vitro* mutagenic potential of latanoprost was tested in bacteria (*Salmonella typhimurium* and *Escherichia coli*) as well as in mouse lymphoma cells. No mutagenic effect was observed in these systems. *In vitro* chromosome aberration studies in human lymphocytes showed an increase in numbers of aberrant cells at concentrations of 130 and 160 µg/mL without of S9 activation, Treatment of cultures with latanoprost in the presence of S9 were negative. Normal frequencies of cells with aberrations were seen at a concentration of 100 µg/mL. The cytotoxic effects of latanoprost were clearly reflected by the poor yield of cells from cultures receiving 160 µg/mL in the absence of S9 activation. The *in vivo* micronucleus test in mice showed no signs of chromosome aberrations. As the aberrations in the mouse lymphoma occurred predominantly in the absence of S9, the performed micronucleus test constitutes an appropriate *in vivo* assessment.	*In vitro* studies did not reveal a mutagenic potential in human.
Carcinogenicity In a study intended to be performed over 80 weeks, mice received latanoprost doses of 2, 20 and 200 µg per kg BW per day (approximately 50, 500 and 5,000 times the human therapeutic dose) administered by gavage route. However, owing to the good survival rate of the animals, the duration of the study was extended until survival had reached approximately 50% for each sex. The males were necropsied week 88, and the females week 92. There were no clinical signs attributable to treatment. Survival was not affected by treatment with latanoprost. The incidence and causes of morbidity and mortality in all groups were consistent with the expected profile in this strain of mouse. There was no indication that red or white blood cell counts were affected by treatment. The spectrum of necropsy findings in treated animals was generally similar to that in controls. There were no non-neoplastic findings of unusual nature or incidence attributable to latanoprost. There were no unusual tumour types or increased incidence of tumours attributable to the drug. It was concluded that latanoprost has no carcinogenic potential in the mouse. The design of the carcinogenicity study in rats was the same as in mice but with longer duration. There were no unusual non-neoplastic findings or increased incidence of tumours attributable to the drug. Thus, oral administration of latanoprost to the rat, for the major part of its life span, at dose levels up to 200 µg per kg	Carcinogenicity studies in mice and rats were negative.

Safety from non- clinical studies	Relevance to human usage
BW per day was well tolerated and produced no evidence of carcinogenic potential.	
Reproductive and development toxicity The fertility and the general reproductive performance were not affected in female or male rats receiving 1 to 10 µg latanoprost per kg BW per day. In the dose range study (1 to 100 µg per kg BW per day) for peri- and postnatal toxicity, pup mortality was increased in the groups given 10 µg per kg BW per day or more and this effect was particularly marked in the 100 µg per kg BW per day group. In rats, no embryotoxicity was observed at the doses of 5, 50 and 250 µg per kg BW per day. Embryolethal effects were seen in rabbits receiving doses above 5 µg per kg BW per day.	Latanoprost has not been found to have any effect on male or female fertility in animal studies. No teratogenic potential has been detected.
References of module SII	***[LATANOPROST] 50 mcg/ml preservative free eye drops, solution*** Module 2.4 Non-clinical overview

SII Conclusions on non-clinical data

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal spec ies. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. High doses of latanoprost, approximately 100 times the cl inical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been sh own to increase the respiration rate probably reflecting bronchoconstriction of short duration. In a nimal studies, latanoprost has not been found to have sensitising properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rab bits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, l atanoprost has been shown to induce increased pigmentation of the iris.The mechanism of increas ed pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also be en shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lym phoma and mouse micronucleus test. Chromosome aberrations were observed *in vitro* with human lymphocytes. Similar effects were observed with prostaglandin F2α, a naturally occurring prostagl

andin, and that indicates a class effect.

Additional mutagenicity studies on *in vitro*/*in vivo* unscheduled DNA synthesis in rats were negati ve and indicate that latanoprost does not have mutagenic potency. Carcinogenicity studies in mice and rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rab bits at doses of 5 micrograms/kg/day and above.

The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant e mbryofoetal toxicity characterised by increased incidence of late resorption and abortion and by r educed foetal weight. No teratogenic potential has been detected.

Module SIII: Clinical trial exposure

SIII.1 Brief overview of development

"[LATANOPROST] 50 mcg/ml preservative free eye drops, solution" is a generic formulation of *XALATAN ® 0,005 % m/V, collyre en solution* (Pfizer). This is being a 'hybrid' application under the Article 10(3) of European Directive 2001/83/EC. Formulations of bimatoprost/timolol have been well established in Europe for more than a decade

SIII.2 Clinical Trial exposure

The clinical efficacy and safety of latanoprost is well known from its extensive use in clinical practice.

Based on the SmPC of the product, outcomes from clinical trials as conducted by the originator are presented below.

Clinical efficacy and safety

Pivotal studies have demonstrated that Latanoprost is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term studies (1 or 2 weeks) suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.
Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.

Paediatric population

The efficacy of Latanoprost in paediatric patients ≤ 18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 50mcg/ml once daily or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in intraocular pressure (IOP) from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to < 3 years, 3 to < 12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 to < 3 years were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 to < 1 year old in the clinical paediatric study. No data are available for preterm infants (less than 36 weeks gestational age).

IOP reductions among subjects in the primary congenital/infantile glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup.

The effect on IOP was seen after the first week of treatment (see graph) and was maintained throughout the 12 week period of study, as in adults.

Table: IOP reduction (mmHg) at week 12 by active treatment group and baseline diagnosis

	Latanoprost N=53	**Timolol N=54**
Baseline Mean (SE)	27.3 (0.75)	27.8 (0.84)
Week 12 Change from Baseline Mean[†] (SE)	-7.18 (0.81)	-5.72 (0.81)

p -value vs. timolol	0.2056			
	PCG N=28	**Non-PCG N=25**	**PCG N=26**	**Non-PCG N=28**
Baseline Mean (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12 Change from Baseline Mean† (SE)	-5.90 (0.98)	-8.66 (1.25)	-5.34 (1.02)	-6.02 (1.18)
p -value vs. timolol	0.6957	0.1317		

SE: standard error.
†Adjusted mean based on an analysis of covariance (ANCOVA) model.

Module SIV: Populations not studied in clinical trials

SIV.1 Limitations of ADR detection common to Clinical Trial Development programmes

Not applicable.

SIV.2 Effect of exclusion criteria in the Clinical Trial Development Plan

Not applicable.

SIV.3 Limitations in respect to populations typically under-represented in Clinical Trial Development programmes

Special populations included in the table below have not been studied in clinical trials. Therefore for these populations *[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* should be either used with caution or it is not recommended.

Special Population	
Pregnant and lactating women	The safety of this medicinal product for use in human pregnancy has not been established. It h as potential hazardous pharmacological effects with respect to the course of pregnancy, to the u nborn or the neonate. Therefore, latanoprost sh ould not be used during pregnancy. Latanoprost and its metabolites may pass into breast milk an d latanoprost should therefore not be used in br east-feeding women or breast feeding should be stopped.
Paediatric patients	Latanoprost eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants

	(less than 36 weeks gestational age). Data in the age group < 1 year (4 patients) are very limited. Long-term safety in children has not yet been established.
Patients with renal impairment	Latanoprost has not been studied in patients wit h renal impairment and should, therefore, be us ed with caution in such patients.
Patients with hepatic impairment	Latanoprost has not been studied in patients wit h hepatic impairment and should, therefore, be used with caution in such patients.
Patients with a history of herpetic keratitis	Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.
Patients patients with known predisposing risk factors for iritis/uveitis	In patients with known predisposing risk factors for iritis/uveitis, latanoprost can be used with caution.
Patients with respiratory disorders	There is limited experience from patients with respiratory disorders, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience.
Use during peri-operative period of cataract surgery	There are limited study data on the use of latanoprost during the peri-operative period of cataract surgery. Latanoprost should be used with caution in these patients.
References	Module 2.5-clinical overview *[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC

SIV.4 Conclusions on the populations not-studies and other limitations of the Clinical Trial Development programme

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

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Patients with renal impairment	NA	Yes
Patients with hepatic impairment	NA	Yes
Patients with a history of herpetic keratitis	NA	Yes
Patients with respiratory disorders	NA	Yes

Module SV: Post-authorisation experience

Since there are no safety concerns regarding the safety and efficacy of "*[LATANOPROST] 50 m cg/ml preservative free eye drops, solution"* based on the post-marketing experience, no post-auth orisation 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

[LATANOPROST] 50 mcg/ml preservative free eye drops, solution is a generic formulation of XALATAN ® *0,005 % m/V, collyre en solution (Pfizer).*

SVI.1 Potential for harm from overdose

The SPC of the product clearly indicates the posology of the active substance. Therefore the possibility for overdose is very limited. Eye drops solution is also contained in a cardboard box, containing a 5 mL white multidose container (HDPE) with pump (PP, HDPE, LDPE) and green pressure cylinder and cap (HDPE). Dropper tip delivers one drop each time. 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. Serious damage to the eye and subsequent loss of vision may result from using contaminated solution. 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. As with other topically-applied ophthalmic agents, the active substance may be absorbed systemically. Latanoprost is a prostaglandin analogue (PGF2a). As plasma concentration is low following topical administration, systemic adverse effects are unlikely to occur. Some common systemic side effects include upper respiratory tract infection/cold/flu, pain in muscle/joint/back, chest pain/angina pectoris, rash/allergic skin reaction.

Based on the established long term use of prostanglandin 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 eye drops 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.

[LATANOPROST] 50 mcg/ml preservative free eye drops, solution , is subject to medical prescription and in the PL of the product it is clearly mentioned that the medicine has been prescribed for a specific patient and must not be passed on to others.

Like other topically applied ophthalmic drugs, is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic prostaglandin analogues. However, incidence of systemic Adverse Drug Reactions (ADRs) after topical ophthalmic administration is lower than for systemic administration.

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

SVI.5 Potential for off-label use

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

The effect of latanoprost on eyelashes was first described by Johnstone in 1997. He described excessive growth of the eyelashes and hair on the skin just below the eye in which latanoprost was used in 43 patients. He noted differences in hair appearance between the latanoprost-treated eye and the untreated eye, including increased number, length, thickness, curvature and pigmentation. The hypertrichotic effect of latanoprost has been used therapeutically. The use of prostaglandin analogues or prostamides as cosmetic eyelash enhancers is becoming more popular. Healthcare professionals should advise that all prescription-only medicines should only be used under medical supervision. This advice is even more applicable when prescription-only medicines are used outside their licensed indications.

SVI.6 Specific paediatric issues

The SPC of the product clearly states in section 4.2 that latanoprost eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants (less than 36 weeks gestational age). Data in the age group < 1 year (4 patients) are very limited.

In children from 0 to < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment. Long-term safety in children has not yet been established.

SVI.7 Conclusions

There is no safety concerns related to this module.

Module SVII: Identified and potential risks

SVII.1 Newly identified safety concerns (since this module was last submitted)

Not applicable.

SVII.2 Recent study reports with implications for safety concerns

Not applicable.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

The active substance latanoprost, a prostaglandin F2α analogue, is a selective prostanoid FP recep tor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration a nd maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at l east 24 hours.

Important Identified Risk	
Hypersensitivity	
Frequency with 95 % CI	Very common (≥1/10)
Seriousness/outcomes	Burning grittiness, itching, stinging and foreign body sensation.
Severity and nature of risk	It is commonly due to an infection (usually viral, but sometimes bacterial) or an allergic reaction. Generally speaking, conjunctivitis will go away on its own and poses no serious health risk.
Background incidence/prevalence	Cannot be determined.
Risk groups or risk factors	Risk increased following long-term treatment with drug
Potential mechanisms	The detailed mechanism of inflammatory response and/or direct toxicity of eye drops has yet to be determined, but it may vary with the different classes of eye drops, different preservatives, and durations of treatments.
Preventability	Ophthalmologist should evaluate the risks and benefits of ophthalmic medications before initiating therapy, identify the minimum dosages necessary to achieve a therapeutic benefit, and monitor patients for local and systemic adverse effects. The use of latanoprost should be avoided in patients with hypersensitivity to latanoprost or to any of the excipients, or with a tendency to develop allergies and asthma.
Impact on individual patient	Deterioration of patient quality of life if treatment with long-term consequences (toxicity)

Important Identified Risk	
Hypersensitivity	
Potential public health impact of safety concern	As well as representing a cosmetic problem for the patient, hyperemia may also compromise the outcome of filtration surgery.
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1; 28(4):267-82. Arici MK, Arici DS, Topalkara A, Güler C. Adverse effects of topical antiglaucoma drugs on the ocular surface. Clin Experiment Ophthalmol. 2000 Apr; 28(2):113-7. M. Detry-Morel, Side effects of glaucoma medications. Bull. Soc. belge Ophtalmol, 299, 27-40, 2006. Penny A. Asbell, Natalia Potapova, Effects of Topical Antiglaucoma Medications on the Ocular Surface. The ocular surface, volume 3, issue 1, January 2005, Pages 27–40. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014.
MedDRA terms	NA

Important Identified Risk	
Eyelash and vellus hair changes	
Frequency with 95 % CI	Very common (≥1/10)
Seriousness/outcomes	Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes.
Severity and nature of risk	Concern related to adverse effects.
Background incidence/prevalence	These adverse events have been reported during post-marketing use of latanoprost in clinical practice and in the literature.
Risk groups or risk factors	Adverse event that may occur in all patients. Vast majority of reports in Japanese population

Important Identified Risk	
Eyelash and vellus hair changes	
Potential mechanisms	The mechanism of eyelash changes and their long term consequences are currently unknown.
Preventability	Eyelash changes are usually reversible upon discontinuation of treatment but conclusive evidence has not been obtained. Patients who have abnormally positioned eyelashes that grow back toward the eye should be monitored for this complication.
Impact on individual patient	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. This side-effect does not have particularly deleterious physicological effects on the patients. In the female patients, the stimulation of lash growth can have a positive psychological effect, as longer thicker lashes are often considered desirable.
Potential public health impact of safety concern	There are certain undesirable physical aspects in this side effect, which can be a permanent source of nuisance, if not a real nuisance to the patient (e.g. the development of a so appreciable lengthening of the eyelashes that periodically may be necessary to cut them, unilateral use of latanoprost).
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 M.Y. Shaikh and Ali A. Bodla. Letter to the Editor: Hypertric hosis of the Eyelashes from Prostaglandin Analog Use: A Ble ssing or a Bother to the Patient?Journal of ocular pharmacolo gy and therapeutics, Volume 22, Number 1, 2006 Holló G. The side effects of the prostaglandin analogues. Exp ert Opin Drug Saf. 2007 Jan;6(1):45-52.
MedDRA terms	NA

Important Identified Risk	
Periorbital skin discolouration	
Frequency with 95 % CI	Rare (≥ 1/10,000 to <1/1,000)
Seriousness/outcomes	Periorbital skin discolouration has been observed with latanoprost use.
Severity and nature of risk	This is a relatively rare side effect of the prostaglandin analogs.
Background incidence/prevalence	The incidence has been reported to be higher with bimatoprost (2.9%) and travoprost (2.9%) than with

Important Identified Risk	
Periorbital skin discolouration	
	latanoprost (1.5%) in one study by Parrish et al.
Risk groups or risk factors	Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients.
Potential mechanisms	The mechanism(s) by which latanoprost causes periocular skin changes are not fully understood. Prostaglandins are important stimulants of melanogenesis, and the FP receptor, to which latanoprost binds, has been localized in all ocular tissue as well as in the hair follicle. In the skin, melanin produced in dermal melanocytes is transported to neighboring keratinocytes in the basal layer of the epidermis. As the keratinocytes ascend to the outer surface, the melanin is partly degraded and then lost as the stratum corneum is sloughed off. This mechanism may explain why latanoprost-induced periocular skin changes are reversible.
Preventability	Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.
Impact on individual patient	This side-effect does not have particularly deleterious physiological effects on the patients.
Potential public health impact of safety concern	It should be recognized that periocular skin seems to be benign, do not pose a known threat to vision or health and of little more than cosmetic consequences.
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 Grierson I, Jonsson M, Cracknell K. Latanoprost and pigmentation. Jpn J Ophthalmol. 2004 Nov-Dec;48(6):602-12. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014.
MedDRA terms	NA

Important Identified Risk	
Iris hyperpigmentation	
Frequency with 95 % CI	Very common (≥1/10)
Seriousness/outcomes	Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Although a final assessment of the clinical significance of prostaglandin-

Important Identified Risk	
Iris hyperpigmentation	
	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	The observed increase in iridial pigmentation does not compr omise the efficacy or safety of the drug nor are other ocular a dverse events associated with the presence of increased iris pi gmentation.
Background incidence/prevalence	Latanoprost instillation for at least 1 year induced increased iris pigmentation in approximately 50% of the treated Japanese eyes, which is a considerably higher percentage than that reported in Caucasians.
Risk groups or risk factors	This 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.
Potential mechanisms	The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish.
Preventability	The observed increase in iridial pigmentation does not compromise the efficacy or safety of the drug nor are other ocular adverse events associated with the presence of increased iris pigmentation. In addition, increased iridial pigmentation appears to be an irreversible or very slowly reversible phenomenon. Caution should be exercised when treating glaucoma only in one eye with prostaglandin analogues (class of medicines to which travoprost belongs).
Impact on individual patient	Latanoprost-induced increases in iris pigmentation do not appear to be related to any underlying or future pathology, cosmetic concerns and ineffective IOP lowering may be the only major reasons for physician and patient decisions to use other ocular hypotensive agents.
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	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014

Important Identified Risk	
Iris hyperpigmentation	
	Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014. Latanoprost-Induced Iris Pigmentation Study Group. Inciden ce of a latanoprost-induced increase in iris pigmentation in Ja panese eyes. Jpn J Ophthalmol. 2006 Mar-Apr;50(2):96-9.
MedDRA terms	NA

Important Identified Risk	
Keratitis herpetic	
Frequency with 95 % CI	Not known
Seriousness/outcomes	Herpetic simplex keratitis, also known as herpetic keratoconjunctivitis and herpesviral keratitis, is a form of keratitis caused by recurrent herpes simplex virus (HSV) infection in the cornea.
Severity and nature of risk	HSV infection is very common in humans. It has been estimated that one third of the world population have recurrent infection. Keratitis caused by HSV is the most common cause of cornea-derived blindness in developed nations. Therefore, HSV infections are a large and worldwide public health problem.
Background incidence/prevalence	Cases reported during post-marketing experience
Risk groups or risk factors	Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.
Potential mechanisms	Antiglaucoma prostaglandin analogues (latanoprost) because of their ability to induce the release of endogenous prostaglandins in the iris and the ciliary muscles may induce re-activation of HSV keratitis. Viral Infection is spread by direct contact of the skin or the mucous membranes to infected secretions.
Preventability	Before prescribing antiglaucoma prostaglandin analogue the healthcare professional should take careful history of any previous herpetic infection.
Impact on individual patient	Keratitis caused by HSV is the most common cause of cornea-derived blindness in developed nations.
Potential public health impact of safety concern	The prognosis in HSV keratitis is generally favorable with aggressive treatment.

Important Identified Risk	
Keratitis herpetic	
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 Soomro MZ, Moin M, Attaulla I. Latanoprost and Herpetic Keratitis. Pak J Ophthalmol 2011, Vol. 27 No. 4.
MedDRA terms	NA

Important Identified Risk	
Cystoid macular oedema	
Frequency with 95 % CI	Rare (≥1/10,000, <1/1000)
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	Reports of macular oedema have occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.
Potential mechanisms	The mechanisms associated with prostaglandins (PG)-induce d intraocular inflammation have not been completely elucidat ed. It has been suggested that PGF2a stimulates the release of PGE2, which in turn stimulates the release of arachidonic aci d by activating phospholipase II. Arachidonic acid may promote the increase of eicosanoids as well as other proinflammatory mediators in the eye,

Important Identified Risk	
Cystoid macular oedema	
	ultimately leading to changes in the blood–aqueous and blood–retinal barriers.
Preventability	Patients who have undergone cataract surgery or other ocular surgery as well as patients with other risk factors for macular oedema, such as ocular (eye) inflammations, diabetes or hypertension (high blood pressure) should avoid use of Latanoprost. If Latanoprost is used in such patients, patients should check their vision frequently and promptly report any change. In case of macular oedema, the medicine should not be used again, to prevent recurrence. The edema resolves, and visual acuity returns, upon cessation of prostaglandin therapy.
Impact on individual patient	Deterioration of patient quality of life due to vision loss.
Potential public health impact of safety concern	Pseudophakic eyes and eyes with other risk factors for macular edema are most likely to be affected, and phakic eyes without risk factors may not be at risk. However, discontinuation of treatment in all populations (at risk or not) should be immediate.
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 Faruk Oztürk MD, Güliz Fatma Yavas MD, Tuncay Küsbeci MD. The Effect of Ocular Hypotensive Agents on Macula. Annals of Ophthalmology October 2007, Volume 39, Issue 4, pp 302-306. ES Arcieri, PTP Pierre Filho, TH Wakamatsu and VP Costa. The effects of prostaglandin analogues on the blood aqueous barrier and corneal thickness of phakic patients with primary open-angle glaucoma and ocular hypertension. Eye (2008) 22, 179–183.
MedDRA terms	NA

Important Identified Risk	
Respiratory disorders	
Frequency with 95 % CI	Rare (≥1/10,000, <1/1000)
Seriousness/outcomes	Dyspnoea (Difficulty to breath), Asthma / Asthma aggravation / Acute asthma attack.
Severity and nature of risk	There is limited experience from patients with asthma but latanoprost neither was found to affect pulmonary function

Important Identified Risk	
Respiratory disorders	
	when studied in a small number of steroid treated patients suffering from moderate asthma nor was it found to affect the pulmonary function, airway reactivity or β2-responsiveness when studied in a small number of non-steroid treated asthma patients.
Background incidence/prevalence	There is limited experience from patients with asthma, but some cases of exacerbation of dyspnoea and/or asthma were reported in post marketing experience.
Risk groups or risk factors	Patients with respiratory problems should be treated with caution until there is sufficient experience.
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 respiratory problems should be advised not to take this product.
Impact on individual patient	Adverse events: Dyspnoea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation
Potential public health impact of safety concern	Prostaglandin's related systemic adverse events occurring via nasopharyngeal mucosal absorption are infrequently seen due to a relatively rapid elimination half-life.
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 M. Detry-Morel. Side effects of glaucoma. Bull. Soc. belge Ophtalmol., 299, 27-40, 2006.
MedDRA terms	NA

Important Identified Risk	
Cardiac disorders	
Frequency with 95 % CI	Very rare (angina unstable - <1/10.000), Uncommon (Angina, palpitations* - ≥1/1.000 to <1/100). * identified post-marketing
Seriousness/outcomes	Cardiac disorders such as angina pectoris (pains to the chest, jaw and back) and chest pain have been reported in association with Latanoprost administration.
Severity and nature of risk	Prostaglandin F2a is a known vasoconstrictor—systemic absorption of latanoprost applied topically can induce

Important Identified Risk	
Cardiac disorders	
	vasoconstriction in coronary vessels, causing angina, especially in patients with unstable angina. Several prostaglandins, including prostaglandin F2a, have been shown to induce hypertrophy of cardiac myocyte in an animal model by the expression of c-fos, atrial natriuretic factor and α skeletal actin. Ventricular hypertrophy can lead to abnormally increased oxygen demand, thereby causing myocardial ischaemia and angina in an already compromised heart.
Background incidence/prevalence	There is limited experience from patients with cardiac disordes, but some cases of angina palpitation were reported in post marketing experience.
Risk groups or risk factors	Patients with cardiac problems should be treated with caution until there is sufficient experience.
Potential mechanisms	Latanoprost applied topically can induce vasoconstriction in coronary vessels, causing angina, especially in patients with unstable angina.
Preventability	Ophthalmologist should evaluate the risks and benefits of ophthalmic medications before initiating therapy. Latanoprost should be used with caution in patients with heart pre-existing disease, due to aggravation of angina and palpitations in these patients.
Impact on individual patient	Adverse events: Angina pectoris, Chest Pain, Palpitations
Potential public health impact of safety concern	Prostaglandin's related systemic adverse events as cardiac disorders are infrequent.
Evidence source	[LATANOPROST] 50 mcg/ml preservative free eye drops, solution SmPC Xalatan Monograph revised on 21 July 2014 Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1; 28(4):267-82. Arici MK, Arici DS, Topalkara A, Güler C. Adverse effects of topical antiglaucoma drugs on the ocular surface. Clin Experiment Ophthalmol. 2000 Apr; 28(2):113-7. M. Detry-Morel, Side effects of glaucoma medications. Bull. Soc. belge Ophtalmol, 299, 27-40, 2006. Penny A. Asbell, Natalia Potapova, Effects of Topical Antiglaucoma Medications on the Ocular Surface. The

Important Identified Risk	
Cardiac disorders	
	ocular surface, volume 3, issue 1, January 2005, Pages 27–40. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014. M Mitra, B Chang, and T James. Exacerbation of angina associated with latanoprost. BMJ. 2001 Oct 6; 323(7316): 783.
MedDRA terms	NA

Important Identified Risk	
Iritis/Uveitis	
Frequency with 95 % CI	Rare (Iritis* - ≥1/10.000 to <1/1.000), Uncommon (Uveitis* – ≥1/1.000 to 1/100 * identified post-marketing
Seriousness/outcomes	Iritis/uveitis. Its course is generally mild and the inflammation resolves upon discontinuation of the medicine with or without anti-inflammatory therapy.
Severity and nature of risk	Uveitis is a condition that involves inflammation of the uveal tract (ie, iris, ciliary body, choroid) or adjacent ocular structures (eg, retina, optic nerve, vitreous, sclera). In most cases, the etiology remains elusive and is often of an autoimmune nature. [1] In instances where the etiology is known, infectious agents or trauma are important causes. Iritis, the most common type of uveitis, affects the front of your eye. The cause is often unknown. It can result from an underlying systemic condition or genetic factor.
Background incidence/prevalence	There is limited experience from patients with iritis/uveitis
Risk groups or risk factors	In patients with known predisposing risk factors for iritis/uveitis.
Potential mechanisms	Prostaglandin-analogues are used to treat open-angle glaucoma and ocular hypertension, and act via increasing uveoscleral outflow. They are the newest class of hypotensive agents and often first-line treatment of glaucoma and ocular hypertension. In one case series, iritis was seen in 4.9% of patients treated with latanoprost within 6 months of starting the medication. This study also reported a 2.1% incidence of cystoid macular edema, with a previous

Important Identified Risk	
Iritis/Uveitis	
	history of CME, iritis, intra-operative vitreous loss, or anterior chamber intraocular lens being risk factors.
Preventability	Latanoprost should be used with caution in patients with a history of iritis/uveitis, or with risk factors for iritis/uveitis. Reinitiating therapy after an episode of iritis/uveitis may not be advisable.
Impact on individual patient	Adverse events iritis/uveitis
Potential public health impact of safety concern	Prostaglandin's related adverse events as iritis/uveitis are infrequent
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 M. Detry-Morel. Side effects of glaucoma. Bull. Soc. belge Ophtalmol., 299, 27-40, 2006. Suominen S, Valimaki J. Bilateral anterior uveitis associated with travoprost. Acta Ophthalmol Scan 84(2): 275-6, 2006
MedDRA terms	NA

Other risks related to the product

Important Potential Risk	
Ocular and cutaneous melanoma	
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-

Important Potential Risk	
Ocular and cutaneous melanoma	
	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. Melanoma was not seen in the clinical trials for latanoprost which studied 462 patients and healthy volunteers. Four cases have been reported in the literature with latanoprost or a member of the same pharmaceutical class: one choroidal melanoma and two cutaneous melanomas associated with latanoprost and one eyelid melanoma associated with bimatoprost (another type of prostaglandin analogue). However, a direct link between prostaglandin analogue use and development of melanoma has never been documented.
Risk groups or risk factors	Some studies suggest that fair skin type is a risk factor for ocular melanoma.
Potential mechanisms	Darkening of the iris is an irreversible side effect of all topical PGF2α analogues. Iris darkening is caused by increased transcription and increased activity of tyrosinase in the iris stromal melanocytes, which is stimulated by clinical dosage of topical PGF2α analogues. Iris darkening does not involve mitotic activity of the melanocytes; thus it does not represent an increased risk for development or progression of uveal malignant melanoma.
Preventability	Patients with fair skin type should be closely monitoring.
Impact on individual patient	Deterioration of patient life
Potential public health impact of safety concern	Potentially life-threatening side effects.
Evidence source	*[LATANOPROST] 50 mcg/ml preservative free eye drops, solution* SmPC Xalatan Monograph revised on 21 July 2014 Ocular Melanoma - Melanoma Research Foundation 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
MedDRA terms	NA

Important Potential Risk	
Risk of ocular overdose	
Frequency with 95 % CI	Cannot be determined

Important Potential Risk	
Risk of ocular overdose	
Seriousness/outcomes	Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.
Severity and nature of risk	One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.
Background incidence/prevalence	Cannot be determined.
Risk groups or risk factors	N/A
Potential mechanisms	N/A
Preventability	N/A
Impact on individual patient	N/A
Potential public health impact of safety concern	N/A
Evidence source	[LATANOPROST] 50 mcg/ml preservative free eye drops, solution SmPC Xalatan Monograph revised on 21 July 2014 Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1; 28(4):267-82. Arici MK, Arici DS, Topalkara A, Güler C. Adverse effects of topical antiglaucoma drugs on the ocular surface. Clin Experiment Ophthalmol. 2000 Apr; 28(2):113-7. M. Detry-Morel, Side effects of glaucoma medications. Bull. Soc. belge Ophtalmol, 299, 27-40, 2006.

Important Potential Risk	
Risk of ocular overdose	
	Penny A. Asbell, Natalia Potapova, Effects of Topical Antiglaucoma Medications on the Ocular Surface. The ocular surface, volume 3, issue 1, January 2005, Pages 27–40. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014.
MedDRA terms	NA

Important Potential Risk	
Off-label use (cosmetic use for stimulation of eyelash growth)	
Frequency with 95 % CI	Eyelash growth: Unknown
Seriousness/outcomes	Latanoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes.
Severity and nature of risk	Concern related to adverse effects.
Background incidence/prevalence	Increase of the length and thickness of the eyelashes (hypertrichosis), as well as darkening of the eyelashes occurs in all races. Reported frequency of eyelashes changes varies between zero and 25% for latanoprost, between 0.7% and 52% for travoprost, and between 3% and 36% for bimatoprost. But in the same population, and using identical criteria for the changes, in studies with a follow-up duration up to six months, the rate was similar for all these three $PGF_{2\alpha}$ analogues. Eyelash changes associated with the use of unoprostone seems to be similar to those observed with latanoprost. Through registered as a side effect, less that 1% of patients complain about hypertrichosis, and many patients in fact prefer the longer lashes, for cosmetic reasons. However, hypertrichosis can lead to complains if it is unilateral, in case of unilateral use of $PGF_{2\alpha}$ analogues. If the topically applied $PGF_{2\alpha}$ analogues use in contact with the eyelids and the malar region, hypertrichosis and hyperpigmentation of the vellus hairs can occur. Discontinuation of $PGF_{2\alpha}$ analogue treatment results in reversal of eyelash pigmentation and hypertrichosis after spontaneous shedding of the lashes or following epilation. As a rare eyelash alteration, poliosis has been described in chronic use of latanoprost, bimatoprost and travoprost.

Important Potential Risk	
Off-label use (cosmetic use for stimulation of eyelash growth)	
Risk groups or risk factors	Adverse event that may occur in all patients.
Potential mechanisms	When prostaglandin and prostamide analogs interact with the prostanoid receptors in the hair follicle, this most likely stimulates the resting follicles (telogen phase) to growing follicles (anagen phase). Prostaglandin and prostamide analogs may also prolong the anagen phase of eyelashes, leading to an increase of eyelash length.
Preventability	Healthcare professionals should advise that all prescription-only medicines should only be used under medical supervision. This advice is even more applicable when prescription-only medicines are used outside their licensed indications.
Impact on individual patient	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Patients must be advised that bimatoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension and should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events.
Potential public health impact of safety concern	Although increased lash length does not have particularly deleterious physicological effects on the patients, bimatoprost is associated with other adverse events, both topical and systemic. This drug must be used under medical supervision and its off-label use for cosmetic purposes should be discouraged.
Evidence source	*[LATANOPROST] 50 mcg/ml + 5 mg/ml, preservative free eye drops, solution*- SmPC M.Y. Shaikh and Ali A. Bodla. Letter to the Editor: Hypertrichosis of the Eyelashes from Prostaglandin Analog Use: A Blessing or a Bother to the Patient?Journal of ocular pharmacology and therapeutics, Volume 22, Number 1, 2006 Holló G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf. 2007 Jan;6(1):45-52. G Holló - Medical Treatment of Glaucoma: The 7th Consensus Report of the World Glaucoma Association, 2010 (book).
MedDRA terms	Growth of eyelashes

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Definitive drug interaction data are not available.

Paediatric population: Interaction studies have only been performed in adults.

SVII.4.2 Important identified and potential interactions

Definitive drug interaction data are not available.

There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

Paediatric population

Interaction studies have only been performed in adults.

Drug-Lifestyle Interactions

Effects on the Ability to Drive and Use Machines

In common with other eye preparations, instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

SVII.5 Pharmacological class effects

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

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

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

Iris hyperpigmentation, punctuate keratitis, bradycardia acute asthma and asthmatic symptoms are pharmacological class effects common to topical prostaglandin use.

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

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

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

SVII.5.2 Important pharmacological class effects not discussed above

Not applicable.

Module SVIII: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Eyelash and vellus hair changes • Periorbital skin discolouration • Iris hyperpigmentation • Keratitis herpetic • Cystoid macular oedema • Respiratory disorders • Cardiac disorders • Iritis / Uveitis
Important potential risks	• Ocular and cutaneous melanoma • Risk of ocular overdose • Off-label use (cosmetic use for stimulation of eyelash growth)
Missing information	• Ocular tolerability in paediatric population • Long-term safety in paediatric population • Limited information on drug interactions in adult and paediatric patients • Use in pregnant and lactating women

PART III: PHARMACOVIGILANCE PLAN

Routine pharmacovigilance Activities

[LATANOPROST] 50mcg/ml preservative free eye drops, solution is a generic formulation. Therefore, routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring. Process followed for '[LATANOPROST] 50mcg/ml preservative free eye drops, solution' under Article 10(3) of European Directive 2001/83/EC, includes collection and medical evaluation of Individual Case Safety Reports (ICSRs), expedited reporting of adverse drug reactions (ADRs), regular signal detection and signal evaluation, weekly screening of the scientific literature for ADR reports, maintenance and administration of the global safety database, preparation and processing of safety reports (e.g PSURs, etc), maintenance of the pharmacovigilance quality management system and standardised processes to define and decide on adequate measures for crisis management and risk minimization.

No additional Pharmacovigilance activities are established for *[LATANOPROST] 50mcg/ml preservative free eye drops, solution*.

III.1 Safety concerns and overview of planned pharmacovigilance actions

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

Hypersensitivity		
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

Eyelash and vellus hair changes		
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

Periorbital skin discolouration		
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

Periorbital skin discolouration		
		currently remains favourable

Iris 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

Keratitis herpetic		
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

Cystoid 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

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

Cardiac 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

Iritis/Uveitis		
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 cutaneous melanoma		
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

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

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

Ocular tolerability in paediatric population		
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

Long-term safety in paediatric population		
Areas requiring	**Proposed routine and**	**Objectives**

Long-term safety in paediatric population		
confirmation or further investigation	**additional PhV activities**	
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

Limited information on drug interactions in adult and paediatric patients		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine Pharmacovigilance	Detection of any changes in risk-benefit balance that currently remains favourable

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

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

Not applicable.

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

Not applicable.

III.4 Details of outstanding additional pharmacovigilance activities

Not applicable.

III.5 Summary of the Pharmacovigilance Plan

Not applicable.

PART IV: PLAN FOR POST-AUTHORISATION EFFICACY STUDIES

"[LATANOPROST] 50 mcg/ml preservative free eye drops, solution" is being an application under Article 10(3) of European Directive 2001/83/EC, as amended.

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

IV.1 Tables of post-authorisation efficacy studies

Not applicable.

IV.2 Summary of post authorisation efficacy development plan

Not applicable.

IV.3 Summary of completed post authorisation efficacy studies

Not applicable.

PART V: RISK MINIMISATION MEASURES

V.1 Routine risk minimisation measures by safety concern

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

Important Identified risk	
Safety concern	**Hypersensitivity**
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 conjunctival hyperaemia is already included in *section 4.8* and *4.9* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.8:*** *Eye Disorders* *Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).* ***Section 4.9:*** *Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the

Important Identified risk	
Safety concern	**Hypersensitivity**
	ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**Eyelash and vellus hair changes**
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 eyelash and vellus hair changes is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.* ***Section 4.8:*** *Eye Disorders* *Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.

Important Identified risk	
Safety concern	**Eyelash and vellus hair changes**
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**Periorbital skin discolouration**
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 periorbital skin discolouration is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.* ***Section 4.8:*** *Eye Disorders* *Rare: local skin reaction on the eyelids; darker colouration of the palpebral skin of the eyelids.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality

Important Identified risk	
Safety concern	**Periorbital skin discolouration**
	metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**Iris 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 iris hyperpigmentation is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.* *This 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. In studies with latanoprost, the onset of the change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation. The iris colour change is slight in the majority of cases and*

Important Identified risk	
Safety concern	**Iris hyperpigmentation**
	often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen. *The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.* *Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, latanoprost treatment may be discontinued.* ***Section 4.8:*** *Eye Disorders* *Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of*

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

Important Identified risk	
Safety concern	**Keratitis herpetic**
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 keratitis herpetic is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.* ***Section 4.8:*** *Infections and Infestations*

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

Important Identified risk	
Safety concern	**Cystoid 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 cystoid macular oedema is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *Reports of macular oedema have occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or*

Important Identified risk	
Safety concern	**Cystoid macular oedema**
	anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema. ***Section 4.8:*** *Eye disorders* *Rare: Iritis; corneal oedema; corneal erosion; periorbital oedema; trichiasis*; distichiasis; iris cyst*§; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**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 aggravation of asthma is already included in *sections 4.4* and *4.8* of the SmPC. In addition it is listed in *sections 2* and *4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.4:*** *There is limited experience from patients with asthma, but some cases of exacerbation of*

Important Identified risk	
Safety concern	**Respiratory disorders**
	asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience. ***Section 4.8:*** *Respiratory, Thoracic and Mediastinal Disorders* *Rare: Asthma, asthma exacerbation and dyspnoea.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**Cardiac disorders**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk

Important Identified risk	
Safety concern	**Cardiac disorders**
Routine risk minimisation measures	Warning on the increased risk of cardiac disorders presented with angina and palpitations as included in section *4.8* of the SmPC. In addition it is listed in *sections 4* of the PL *(*Possible side effects). ***Section 4.8:*** *Cardiac Disorders:* *Uncommon: Angina; palpitations* *Very rare: Angina unstable* ***Section 4.8:*** Uncommon: • *Chest pain (angina), awareness of heart rhythm (palpitations).* Very rare: • *Worsening of angina in patients who also have heart disease, sunken eye appearance (eye sulcus deepening).*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Identified risk	
Safety concern	**Iritis/Uveitis**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the

Important Identified risk	
Safety concern	**Iritis/Uveitis**
	risk
Routine risk minimisation measures	Warning on the increased risk of choroidal detachment is already included in *sections 4.8* of the SmPC. In addition it is listed in *section 4* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.8:*** *Eye disorders* *Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Potential risk	
Safety concern	**Ocular and cutaneous melanoma**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Warning on the potential risk of ocular and cutaneous melanoma is already included in *section 5.3* of the SmPC. ***Section 5.3:*** *The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.Carcinogenicity studies in mice and rats were negative.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Potential risk	
Safety concern	**Risk of ocular overdose**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk

Important Potential risk	
Safety concern	**Risk of ocular overdose**
Routine risk minimisation measures	The warning on the risk of overdose and related adverse reactions is listed in section 4.9 of the SPC. In addition, it is listed in the PL, section 3 (risk communication to reduce the incidence of it).. ***Section 4.9*** *Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.* *If [Invented name] is accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.* *Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.* *If overdosage with [Invented name] occurs, treatment should be symptomatic.* PL section 3. 3.How to use [Invented name] *Always use this medicine exactly as your doctor*

Important Potential risk	
Safety concern	**Risk of ocular overdose**
	or the doctor treating your child has told you. Check with your doctor, the doctor treating your child or pharmacist if you are not sure. *The recommended dose for adults (including the elderly) and children is one drop once a day in the affected eye(s). The best time to do this is in the evening.* *Do not use [Invented name] more than once a day, because the effectiveness of the treatment can be reduced if you administer it more often.* *Use [Invented name] as instructed by your doctor or by the doctor treating your child until they tell you to stop.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Important Potential risk	
Safety concern	**Off-label use (cosmetic use for stimulation of eyelash growth)**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk

Important Potential risk	
Safety concern	**Off-label use (cosmetic use for stimulation of eyelash growth)**
Routine risk minimisation measures	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Latanoprost should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events. Warning on this risk is already included in *section 4.8* of SmPC. It is also listed in *section 4* of PIL (risk communication to reduce the incidence of it) ***Section 4.1:*** *Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.* ***Section 4.8:*** *Eye disorders* Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus **Section 4:** Eye Disorders: Changes to the eyelashes and fine hairs around the eye (increased number, length, thickness and darkening), changes to the direction of eyelash growth, swelling around the eye, swelling of the coloured part of the eye (iritis/uveitus), swelling at the back of the eye (macular oedema), inflammation/irritation of the surface of the eye (keratitis), dry eyes, fluid filled cyst within the coloured part of the eye (iris cyst), light sensitivity

Important Potential risk	
Safety concern	**Off-label use (cosmetic use for stimulation of eyelash growth)**
	(photophobia), sunken eye appearance (deepening of the eye sulcus).
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None Proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Missing information	
Safety concern	**Ocular tolerability in paediatric population**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Information concerning limited data of ocular tolerability in paediatric population is already included in *section 4.4* of the SmPC. ***Section 4.4:*** *Efficacy and safety data in the age group < 1 year (4 patients) are very limited (see section 5.1). No data are available for preterm infants (less than 36 weeks gestational age).* *In children from 0 to < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.*

Missing information	
Safety concern	**Ocular tolerability in paediatric population**
	Long-term safety in children has not yet been established.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Missing information	
Safety concern	**Long-term safety in paediatric population**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Information concerning limited data on long-term safety in paediatric population is already included in *section 4.4* of the SmPC. ***Section 4.4:*** *Paediatric population* *Efficacy and safety data in the age group < 1 year (4 patients) are very limited. No data are available for preterm infants (less than 36 weeks gestational age). In children from 0 to < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment. Long-term safety in children has not yet been established.*

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

Missing information	
Safety concern	**Limited information on drug interactions in adult and paediatric patients**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Information concerning limited data on drug interactions in adult and paediatric patients is already included in *section 4.5* of the SmPC. In addition it is listed in *section 2* of the PL *(*risk communication to reduce the incidence of it). ***Section 4.5:*** *Definitive drug interaction data are not available. There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.* <u>*Paediatric population*</u> *Interaction studies have only been performed in adults.*

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

Missing information	
Safety concern	**Use in pregnant and lactating women**
Objective(s) of the risk minimisation measures	Making aware of physicians and monitoring the risk
Routine risk minimisation measures	Information concerning limited data on latanoprost use in pregnant and lactating women is already included in *section 4.6* of the SmPC. In addition it is listed in *section 2* of the PL *(*risk communication to reduce the incidence of it) ***Section 4.6:*** *Fertility* *Latanoprost has not been found to have any effect on male or female fertility in animal studies.* *<u>Pregnancy</u>* *The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore,*

Missing information	
Safety concern	**Use in pregnant and lactating women**
	latanoprost should not be used during pregnancy. *<u>Lactation</u>* *Latanoprost and its metabolites may pass into breast milk and latanoprost should therefore not be used in breast-feeding women or breast feeding should be stopped.*
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Assessment of the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	Routine assessment of the overall performance of the Pharmacovigilance system using quality metrics.
Planned dates for assessment	Assessment takes place routinely through the ongoing pharmacovigilance activities. Periodic assessments
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

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**
Hypersensitivity	SmPC sections 4.8 and 4.9 PIL section 4 Prescription only medicine	None proposed
Eyelash and vellus hair changes	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed

Periorbital skin discolouration	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Iris hyperpigmentation	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Keratitis herpetic	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Cystoid macular oedema	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Respiratory disorders	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Cardiac disorders	SmPC sections 4.8 PIL section 4 Prescription only medicine	None proposed
Iritis/Uveitis	SmPC sections 4.8 PIL sections 4 Prescription only medicine	None proposed
Ocular and cutaneous melanoma	SmPC sections 5.3 Prescription only medicine	None proposed
Risk of ocular overdose	SmPC section 4.9 Prescription only medicine	None proposed
Off-label use (cosmetic use for stimulation of eyelash growth)	SmPC sections 4.8 PIL sections 4 Prescription only medicine	None proposed
Ocular tolerability in paediatric population	SmPC section 4.4 Prescription only medicine	None proposed
Long-term safety in paediatric population	SmPC section 4.4 Prescription only medicine	None proposed
Limited information on drug interactions in adult and paediatric patients	SmPC sections 4.5 PIL section 2 Prescription only medicine	None proposed
Use in pregnant and lactating women	SmPC sections 4.6 PIL section 2 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	• Hypersensitivity • Eyelash and vellus hair changes • Periorbital skin discolouration • Iris hyperpigmentation • Keratitis herpetic • Cystoid macular oedema • Respiratory disorders • Cardiac disorders • Iritis/uveitis
Important potential risks	• Ocular and cutaneous melanoma • Risk of ocular overdose • Off-label use (cosmetic use for stimulation of eyelash growth)
Missing information	• Ocular tolerability in paediatric population • Long-term safety in paediatric population • Limited information on drug interactions in adult and paediatric patients • Use in pregnant and lactating women

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

Not applicable.

VI.1.3 Tables of post-authorisation efficacy studies

Not applicable.

VI.1.4 Summary of risk minimisation measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**

Hypersensitivity	SmPC sections 4.8 and 4.9 PIL section 4 Prescription only medicine	None proposed
Eyelash and vellus hair changes	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Periorbital skin discolouration	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Iris hyperpigmentation	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Keratitis herpetic	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Cystoid macular oedema	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Repsiratory disorder	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Cardiac disorder	SmPC sections 4.8 PIL sections 4 Prescription only medicine	None proposed
Iritis/Uveitis	SmPC sections 4.8 PIL sections 4 Prescription only medicine	None proposed
Ocular and cutaneous melanoma	SmPC sections 4.4 and 5.3 Prescription only medicine	None proposed
Risk of ocular overdose	SmPC section 4.9 Prescription only medicine	None proposed
Off-label use (cosmetic use for stimulation of eyelash growth)	SmPC sections 4.8 PIL sections 4 Prescription only medicine	None proposed
Ocular tolerability in paediatric population	SmPC section 4.4 Prescription only medicine	None proposed
Long-term safety in paediatric population	SmPC section 4.4 Prescription only medicine	None proposed
Limited information on drug interactions in adult and paediatric patients	SmPC sections 4.5 PIL section 2 Prescription only medicine	None proposed
Use in pregnant and lactating women	SmPC sections 4.6 PIL section 2 Prescription only medicine	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

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. 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

Latanoprost belongs to a group of medicines known as prostaglandin analogues. It works by increasing the natural outflow of fluid from inside the eye into the bloodstream. Latanoprost is used to treat conditions known as open angle glaucoma and ocular hypertension in adults. Both of these conditions are linked with an increase in the pressure within your eye, eventually affecting your eye sight. Latanoprost is also used to treat increased eye pressure and glaucoma in all ages of children and babies.

The safety and efficacy of latanoprost in adult patients with elevated eye pressure is supported by more than 13 years of clinical experience.

VI.2.3 Unknowns relating to treatment benefits

The treatment benefit of latanoprost has not been studied in the following populations/patients:

- **Pregnant and breast-feeding women**;

The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, latanoprost should not be used during pregnancy. Latanoprost and its metabolites may pass into breast milk and latanoprost should therefore not be used in breast-feeding women or breast feeding should be stopped.

- **Patients with kidney disease**;

Latanoprost has not been studied in patients with renal impairment and should, therefore, be used with caution in such patients.

- **Patients with liver disease**.

Latanoprost has not been studied in patients with hepatic impairment and should, therefore, be used with caution in such patients.

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Allergic reaction *(Hypersensitivity)*	Eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye).The ocular side effect appears to occur via a secondary, unrelated mechanism.	If you experience eye irritation severe enough to make your eyes water excessively, or make you consider stopping this medicine, talk to your doctor, pharmacist or nurse promptly (within a week). You may need your treatment to be reviewed to ensure you keep receiving appropriate treatment for your condition.
Increase of the length, thickness, colour and/or number of the eyelashes that may cause unusual hair growth on the eyelids. *(Eyelash and vellous hair changes)*	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.
Darkening of the skin around the eyes. *(Periorbital skin discolouration)*	Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients.	Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.
Change in the colour of iris	Latanoprost may gradually	These changes are solely

(the coloured part of the eye). *(Iris hyperpigmentation)*	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.	cosmetic in nature, and have not posed a health risk in any form. However, an ophthalmologist should be advised.
Inflammation or irritation of the surface of the eye. *(Keratitis herpetic)*	Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.	Before prescribing antiglaucoma prostaglandin analogue the healthcare professional should take careful history of any previous herpetic infection.
Thickening of oval-shaped pigmented area near the center of the inner coat of the eye *(Cystoid macular oedema)*	Macular oedema has occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.	Before prescribing antiglaucoma prostaglandin analogue the healthcare professional should take careful history of diabetic retinopathy and retinal vein occlusion. Latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses
Breathing disorders *(Respiratory disorders)*	There is limited experience from patients with respiratory disorders, mainly with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience.	Patients with respiratory problems should therefore be treated with caution until there is sufficient experience.
Heart disorders	Several prostaglandins, including prostaglandin F2a,	Warning on the increased risk of cardiac disorders presented

(Cardiac disorders)	have been shown to induce hypertrophy of cardiac myocyte in an animal model by the expression of c-fos, atrial natriuretic factor and α skeletal actin.3 Ventricular hypertrophy can lead to abnormally increased oxygen demand, thereby causing myocardial ischaemia and angina in an already compromised heart.	with angina and palpitations as included in section 4.8 of the SmPC.
Inflammation of the iris and/or the uvea of the eye (Iritis/Uveitis	Uveitis is a condition that involves inflammation of the uveal tract (ie, iris, ciliary body, choroid) or adjacent ocular structures (eg, retina, optic nerve, vitreous, sclera). In most cases, the etiology remains elusive and is often of an autoimmune nature. In instances where the etiology is known, infectious agents or trauma are important causes. Iritis, the most common type of uveitis, affects the front of your eye. The cause is often unknown. It can result from an underlying systemic condition or genetic factor.	Patients with a history of iritis/uveitis or with risk factors for iritis/uveitis should use product with caution. Reinitiating therapy after an episode of iritis/uveitis may not be advisable.

Important potential risks	
Risk	**What is known (Including reason why it is considered a pote ntial risk)**
Risk of ocular overdose	Apart from ocular irritation and conjunctival hyperaemia, no ot her ocular side effects are known if latanoprost is overdosed. Int ravenous administration of latanoprost in monkeys has been ass ociated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not i nduced by latanoprost when applied topically on the eyes in a d ose of seven times the clinical dose of latanoprost.
Ocular and cutaneous melanoma	Cancers of the eye and skin have been reported in patients treated with latanoprost. However, no causal relationship has been established between the use of latanoprost and these

	cancers. Also, no potential for causing cancer has been observed in animal studies performed with latanoprost.
Off-label use (cosmetic use for stimulation of eyelash growth)	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Patients must be advised that Latanoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension and should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events.

Missing information	
Risk	**What is known**
Ocular tolerability in paediatric population	Latanoprost may cause eye irritation. Patients who already have medical conditions affecting the cornea may be more susceptible to develop irritation.
Long-term safety in paediatric population	There is limited information on the long term effect of latanoprost in paediatric patients.
Limited information on drug interactions in adult and paediatric patients	Definitive drug interaction data are not available. There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended. *Paediatric population* Interaction studies have only been performed in adults.
Use in pregnant and lactating women	*Pregnancy* The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, latanoprost should not be used during pregnancy. *Lactation* Latanoprost and its metabolites may pass into breast milk and latanoprost should therefore not be used in breast-feeding women or breast feeding should be stopped.

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	27.04.2017	**Important identified risks** • Hypersensitivity • Eyelash and vellus hair changes • Periorbital skin discolouration • Iris hyperpigmentation • Keratitis herpetic • Cystoid macular oedema • Respiratory disorders • Cardiac disorders • Iritis/Uveitis **Important potential risks** • Ocular and cutaneous melanoma • Risk of ocular overdose • Off-label use (cosmetic use for stimulation of eyelash growth) **Missing information** • Ocular tolerability in paediatric population • Long-term safety in paediatric population • Limited information on drug interactions in adult and paediatric patients • Use in pregnant and lactating women	Initial version

PART VII: ANNEXES

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ANNEX 1 – EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2 - SMPC & PACKAGE LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 50 micrograms/mL eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 50 micrograms of latanoprost.

Excipient with known effect
Each mL of solution contains 25 mg Macrogolglycerol hydroxystearate 40 (see section 4.4.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colorless, aqueous solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.

Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.

4.2 Posology and method of administration

Posology

Adults (including the elderly)
Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if [Invented name] is administered in the evening.

The dosage of [Invented name] should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as normal.

Paediatric population

[Invented name] eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants (less than 36 weeks gestational age). Data in the age group < 1 year (4 patients) are limited (see section 5.1).

Method of administration

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.

If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least five minutes apart.

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

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

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.

This 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. In studies with latanoprost, the onset of the change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.8). The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence.

In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, latanoprost treatment may be discontinued.

There is limited experience of latanoprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of latanoprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Latanoprost has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that [Invented name] should be used with caution in these conditions until more experience is obtained.

There are limited study data on the use of latanoprost during the peri-operative period of cataract surgery. [Invented name] should be used with caution in these patients.

[Invented name] should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Reports of macular oedema have occurred (see section 4.8) mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). [Invented name] should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

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

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience, see also section 4.8.

Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Paediatric population

Efficacy and safety data in the age group < 1 year (4 patients) are very limited (see section 5.1). No data are available for preterm infants (less than 36 weeks gestational age).

In children from 0 to < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

Long-term safety in children has not yet been established.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Definitive drug interaction data are not available.

There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of latanoprost for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, [Invented name] should not be used during pregnancy.

Breast-feeding

Latanoprost and its metabolites may pass into breast milk and [Invented name] should therefore not be used in breast-feeding women or breast-feeding should be stopped.

Fertility

Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

In common with other eye preparations, instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The majority of adverse reactions relate to the ocular system. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse reactions are generally transient and occur on dose administration.

Tabulated list of adverse reactions

Adverse reactions are categorized by frequency as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to < 1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**
Infections and infestations				Herpetic keratitis*§	
Nervous system disorders			Headache*; dizziness*		

Eye disorders	Iris hyperpigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes)	Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis *	Eyelid oedema; dry eye; keratitis*; vision blurred; macular oedema including cystoid macular oedema*; uveitis*	Iritis*; corneal oedema*; corneal erosion; periorbital oedema; trichiasis*; distichiasis; iris cyst*§; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva*§	Periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders			Angina; palpitations*		Angina unstable
Respiratory, thoracic and mediastinal disorders			Asthma*; dyspnoea*	Asthma exacerbation	
Skin and subcutaneous tissue disorders			Rash	Pruritus	
Musculoskeletal and connective tissue disorders			Myalgia*; arthralgia*		
General disorders and administration site conditions			Chest pain*		

*ADR identified post-marketing

§ADR frequency estimated using "The Rule of 3"

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

Description of selected adverse reactions

No information is provided.

Paediatric population

In two short term clinical trials (≤ 12 weeks), involving 93 (25 and 68) paediatric patients the safety profile was similar to that in adults and no new adverse events were identified. The short term safety profiles in the different paediatric subsets were also similar (see section 5.1). Adverse events seen more frequently in the paediatric population as compared to adults are: nasopharyngitis and pyrexia.

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

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if latanoprost is overdosed.

If [Invented name] is accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.

Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.

If overdosage with [Invented name] occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues, ATC code: S01EE01

Mechanism of action

The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.

Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Pharmacodynamic effects

Pivotal studies have demonstrated that latanoprost is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

Latanoprost in clinical doses has not been found to have any significant pharmacological effect on the cardiovascular or respiratory system.

Paediatric population

The efficacy of latanoprost in paediatric patients ≤ 18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 50 micrograms/mL once daily

or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in intraocular pressure (IOP) from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to <3 years, 3 to < 12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 to < 3 years were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 to < 1 year old in the clinical paediatric study. No data are available for preterm infants (less than 36 weeks gestational age).

IOP reductions among subjects in the primary congenital/infantile glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup.

The effect on IOP was seen after the first week of treatment (see table) and was maintained throughout the 12 week period of study, as in adults.

Table: IOP reduction (mmHg) at week 12 by active treatment group and baseline diagnosis				
	Latanoprost N=53		**Timolol N=54**	
Baseline Mean (SE)	27.3 (0.75)		27.8 (0.84)	
Week 12 Change from Baseline Mean[†](SE)	-7.18 (0.81)		-5.72 (0.81)	
p-value vs. timolol	0.2056			
	PCG N=28	**Non-PCG N=25**	**PCG N=26**	**Non-PCG N=28**
Baseline Mean (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12 Change from Baseline Mean[†](SE)	-5.90 (0.98)	-8.66 (1.25)	-5.34 (1.02)	-6.02 (1.18)
p-value vs. timolol	0.6957	0.1317		

SE: standard error.

[†]Adjusted estimate based on an analysis of covariance (ANCOVA) model.

5.2 Pharmacokinetic properties

Latanoprost (MW 432.58) is an isopropyl ester prodrug which per se is inactive, but, after hydrolysis to the acid of latanoprost, becomes biologically active.

The prodrug is well absorbed through the cornea and all active substance that enters the aqueous humour is hydrolysed during the passage through the cornea.

Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of the active substance reach the posterior segment.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The half-life in plasma is 17 minutes in man. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Paediatric population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 micrograms/mL, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to < 12 year olds and 6-fold higher in children < 3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained (see section 4.9). Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (< 20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

5.3 Preclinical safety data

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In animal studies, latanoprost has not been found to have sensitising properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris.

The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed *in vitro* with human lymphocytes. Similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, and indicates that this is a class effect.

Additional mutagenicity studies on *in vitro/in vivo* unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency. Carcinogenicity studies in mice and rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits at doses of 5 micrograms/kg/day and above.

The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant embryofoetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight.

No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate 40
Sodium chloride
Disodium edetate
Sodium dihydrogen phosphate dihydrate
Anhydrous disodium phosphate
Hydrochloric acid or/and Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost. If such medicinal products are used, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

18 months
4 weeks after first opening

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

DK/H/2754/001/DC
[Invented name] is presented as a 2.5 mL clear, colorless, aqueous solution, in a cardboard box containing a 5 mL white multidose container (HDPE) with pump (PP, HDPE, LDPE) and orange pressure cylinder and cap (HDPE).

DK/H/2755/001/DC
[Invented name] is presented as a 2.5 mL clear, colorless, aqueous solution, in a cardboard box containing a 5 mL white multidose container (HDPE) with pump (PP, HDPE, LDPE) and green pressure cylinder and cap (HDPE).

Pack sizes: [X] number of bottles of 2.5 mL solution

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

Package leaflet: Information for the user

[Invented name] 50 micrograms/mL eye drops, solution
latanoprost

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, the doctor treating your child or pharmacist.
- This medicine has been prescribed for you or for your child 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 or your child get any side effects, talk to your doctor, the doctor treating your child or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

[Invented name] belongs to a group of medicines known as prostaglandin analogues. It works by increasing the natural outflow of fluid from inside the eye into the bloodstream.

[Invented name] is used to treat conditions known as **open angle glaucoma** and **ocular hypertension** in adults. Both of these conditions are linked with an increase in the pressure within your eye, eventually affecting your eye sight.

[Invented name] is also used to treat increased eye pressure and glaucoma in all ages of children and babies.

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

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

[Invented name] can be used in adult men and women (including the elderly) and in children from birth to 18 years of age. [Invented name] has not been investigated in prematurely born infants (less than 36 weeks gestation).

Do not use [Invented name]:

- If you are allergic to latanoprost or any of the other ingredients of this medicine (listed in section 6).
- If you are pregnant or trying to become pregnant.
- If you are breast-feeding.

Warnings and precautions

Talk to your doctor, the doctor treating your child or pharmacist before using [Invented name] or before you give this to your child if you think any of the following apply to you or your child:

- If you or your child are about to have or have had eye surgery (including cataract surgery)
- If you or your child suffer from eye problems (such as eye pain, irritation or inflammation, blurred vision)
- If you or your child suffer from dry eyes
- If you or your child have severe asthma or the asthma is not well controlled
- If you have suffered or are currently suffering from a viral infection of the eye caused by the herpes simplex virus (HSV)

Other medicines and [Invented name]

[Invented name] may interact with other medicines. Tell your doctor, the doctor treating your child or pharmacist if you or your child are using, have recently used or might use any other medicines, including those medicines (or eye drops) obtained without a prescription.

Pregnancy and breast-feeding

Do not use [Invented name] when you are pregnant or breast-feeding.

Tell your doctor immediately if you are pregnant, think you may be pregnant or are planning to have a baby.

Driving and using machines

When you use [Invented name] you might have blurred vision, for a short time. If this happens to you, do not drive or use any tools or machines until your vision becomes clear again.

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

3. How to use [Invented name]

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

The recommended dose for adults (including the elderly) and children is one drop once a day in the affected eye(s). The best time to do this is in the evening.

Do not use [Invented name] more than once a day, because the effectiveness of the treatment can be reduced if you administer it more often.

Use [Invented name] as instructed by your doctor or by the doctor treating your child until they tell you to stop.

Instructions for use

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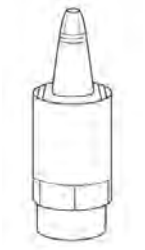
<td> 
1a
 
1b</td>
<td>

- Take the multidose container **(picture 1a)** out of the carton box and write the date of opening on the carton box and the bottle in the space provided.
- Get the medicine bottle and a mirror.
- Wash your hands.
- Remove the cap **(picture 1b)**.

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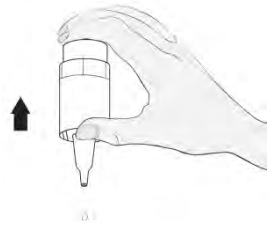
<td> 
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- Hold the bottle upside down with the thumb on the shoulder of the bottle and the other fingers on the bottom of the bottle. Before the first use, pump the bottle repeatedly, approximately 10 times, until the first drop emerges **(picture 2)**.

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- Tilt your head or your child's head back. Pull down the eyelid with a clean finger, until there is a 'pocket' between the eyelid and the eye. The drop will go in here **(picture 3)**.
- Bring the bottle tip close to the eye. Use the mirror if it helps.

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</tr>
</table>

 **4**	• **Do not touch the eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops. • Gently press down on the bottom side of the bottle to release one drop of medicine at a time **(picture 4)**. • If a drop misses the eye, try again.
 **5**	• After using the medicine, press a finger into the corner of the eye, by the nose, for 1 minute **(picture 5)**. This helps to stop the medicine getting into the rest of the body.
	• If you use drops in both eyes, repeat these same steps for the other eye. • Close the multidose container cap firmly immediately after use. • Only use one bottle of medicine at a time. Do not open the cap until you need to use the multidose container. • **You must throw away the bottle 4 weeks after you first opened it,** to prevent infections, and use a new bottle.

If you use [Invented name] with other eye drops

Wait at least 5 minutes between using [Invented name] and using other eye drops.

If you use more [Invented name] than you should

If you put too many drops into the eye, it may lead to some minor irritation in the eye and the eyes may water and turn red. This should pass, but if you are worried contact your doctor or the doctor treating your child for advice.

Contact your doctor as soon as possible if you or your child swallows [Invented name] accidentally.

If you forget to use [Invented name]

Carry on with the usual dosage at the usual time. Do not use a double dose to make up for a forgotten dose. If you are unsure about anything talk to your doctor or pharmacist.

If you stop using [Invented name]

You should speak to your doctor or the doctor treating your child if you want to stop using [Invented name].

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.

The following are known side effects of using eye drops containing the active substance latanoprost:

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

- A gradual change in your eye colour by increasing the amount of brown pigment in the coloured part of the eye known as the iris. If you have mixed-colour eyes (blue-brown, grey-brown, yellow-brown or green-brown) you are more likely to see this change than if you have eyes of one colour (blue, grey, green or brown eyes). Any changes in your eye colour may take years to develop although it is normally seen within 8 months of treatment. The colour change may be permanent and may be more noticeable if you use [Invented name] in only one eye. There appears to be no problems associated with the change in eye colour. The eye colour change does not continue after [Invented name] treatment is stopped.
- Redness of the eye.
- Eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye). If you experience eye irritation severe enough to make your eyes water excessively, or make you consider stopping this medicine, talk to your doctor, pharmacist or nurse promptly (within a week). You may need your treatment to be reviewed to ensure you keep receiving appropriate treatment for your condition.
- A gradual change to eyelashes of the treated eye and the fine hairs around the treated eye, seen mostly in people of Japanese origin. These changes involve an increase of the colour (darkening), length, thickness and number of your eye lashes.

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

- Irritation or disruption to the surface of the eye, eyelid inflammation (blepharitis), eye pain, light sensitivity (photophobia), conjunctivitis.

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

- Eyelid swelling, dryness of the eye, inflammation or irritation of the surface of the eye (keratitis), blurred vision, inflammation of the coloured part of the eye (uveitis), swelling of the retina (macular oedema).
- Skin rash.
- Chest pain (angina), awareness of heart rhythm (palpitations).
- Asthma, shortness of breath (dyspnoea).
- Chest pain.
- Headache, dizziness.
- Muscle pain, joint pain.

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

- Inflammation of the iris (iritis), symptoms of swelling or scratching/damage to the surface of the eye, swelling around the eye (periorbital oedema), misdirected eyelashes or an extra row of eyelashes, scarring of the surface of the eye, fluid filled area within the coloured part of the eye (iris cyst).
- Skin reactions on the eyelids, darkening of the skin of the eyelids.
- Worsening of asthma.
- Severe itching of the skin.
- Developing a viral infection of the eye caused by the herpes simplex virus (HSV).

Very rare (may affect up to 1 in 10,000 people):

- Worsening of angina in patients who also have heart disease, sunken eye appearance (eye sulcus deepening).

Side effects seen more often in children compared to adults are runny itchy nose and fever.

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

Reporting of side effects

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

5. How to store [Invented name]

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

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

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 the bottle label and box.

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

6. Contents of the pack and other information

What [Invented name] contains

- The active substance is latanoprost.
  Each mL of [Invented name] contains 50 micrograms of latanoprost.
- The other ingredients are macrogolglycerol hydroxystearate 40, sodium chloride, disodium edetate, sodium dihydrogen phosphate dihydrate, anhydrous disodium phosphate, hydrochloric acid or/and sodium hydroxide (for pH adjustment), water for injections

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

DK/H/2754/001/DC

[Invented name] is presented as a 2.5 mL clear, colorless, aqueous solution, free from visible particles in a cardboard box containing a 5 mL white multidose container (HDPE) with pump (PP, HDPE, LDPE) and orange pressure cylinder and cap (HDPE).

DK/H/2755/001/DC

[Invented name] is presented as a 2.5 mL clear, colorless, aqueous solution, free from visible particles in a cardboard box containing a 5 mL white multidose container (HDPE) with pump (PP, HDPE, LDPE) and green pressure cylinder and cap (HDPE).

Pack sizes:
Cartons containing [X] number of bottles of 2.5 mL solution

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last revised in <{MM/YYYY}>

<[To be completed nationally]>

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 I V

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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