Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for Summary Tables in the EPAR

VI.1.1. Summary Table of Safety Concerns

Table 51. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Conjunctival hyperaemia • Eyelash and vellus hair changes • Periorbital skin discoloration • Iris hyperpigmentation • Keratitis herpetic
Important potential risks	• Cystoid macular oedema • Aggravation of asthma
Missing information	• Long term safety in paediatric patients (including ocular developmental and neurodegenerative events, hyperpigmentation changes in the eye, and corneal endothelial function/corneal thickness) • Ocular tolerability in paediatric population • Limited information on drug interactions in adult and paediatric patients • Use in pregnant and lactating women

VI.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Table 52. Ongoing and Planned Studies

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned/Started)**	**Date for Submission of Final Study Report (Planned or Actual)**
A6111144 Long-term surveillance study to monitor hyperpigmentation changes in the eye in paediatric populations. (extension of Study A6111143)	To describe the incidence (proportion and rate) of hyperpigmentation changes in the eye over a total of 10-year follow up period by combining the data collected in the 3-year A6111143 study, and the subsequent 7-year A6111144 study, among paediatric patients with glaucoma or elevated IOP who have completed the 3-year cohort study	Long-term ocular and systemic safety in the paediatric population	Ongoing FSFV date: 10 March 2014	Projected study report: 2024

Table 52. Ongoing and Planned Studies

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
	(A6111143).			

FSFV = first subject first visit; IOP = intraocular pressure

VI.1.3. Summary of Post-Authorisation Efficacy Development Plan

Not applicable.

VI.1.4. Summary Table of Risk Minimisation Measures

Table 53. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Conjunctival Hyperaemia	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients	None
Eyelash and Vellus Hair Changes	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients	None
Periorbital Skin Discoloration	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients	None
Iris Hyperpigmentation	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients	None
Keratitis herpetic	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients	None
Important potential risks		
Cystoid Macular Oedema	Prescribing information in the SmPC advises patients and prescribers to the possible occurrence of these events in patients with known risk factors for macular oedema.	None
Aggravation of Asthma	Prescribing information in the SmPC advises patients and prescribers that there is limited information from patients with asthma and some cases of exacerbation of asthma have been noted.	None
Missing information		

Table 53. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Ocular tolerability in paediatric population	Prescribing information in the SmPC informs patients and prescribers that long term safety in children has not been established	None proposed.
Long term safety in paediatric patients (including ocular developmental and neurodegenerative events, hyperpigmentation changes in the eye, and corneal endothelial function/corneal thickness)	Prescribing information in the SmPC informs patients and prescribers that long term safety in children has not been established.	None proposed.
Limited information on drug interactions in adult and paediatric patients	Prescribing information in the SmPC informs patients and prescribers that information regarding drug interactions in paediatric patients is limited.	None proposed.
Use in pregnant and lactating women	Prescribing information in the SmPC informs patients and prescribers that latanoprost should not be used during pregnancy and/or lactation.	None proposed.

SmPC = Summary of Product Characteristics.

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Glaucoma is the second leading cause of blindness worldwide, and affects about 66.8 million people worldwide.[1,2] Glaucoma can affect individuals at any age, but it is more common with increasing age, black or Hispanic ethnicity (compared with white ethnicity), and females more than males in the adult form of the condition.[4] The estimated incidence of OAG (a form of glaucoma) is 1/1000 per year in white individuals, and 5.5/1000 per year in black individuals.[6,7] In its infantile form, more males are affected by this condition than females.[90]

Paediatric or childhood glaucomas constitute a rare, varied group of conditions which can present at different ages during childhood.[8] The incidence of paediatric glaucoma varies considerably across the world.[9] Data from studies in Western countries suggest that the incidence of infantile primary glaucoma ranges from 1:10,000 to 20,000 live births.

VI.2.2. Summary of Treatment Benefits

Latanoprost belongs to a group of medicines known as PGAs. It works by increasing the natural outflow of fluid from inside the eye into the bloodstream. Latanoprost is used to treat conditions known as OAG and OHT in adults. Both of these conditions are linked with an increase in the pressure within the eye, eventually affecting 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. The efficacy of latanoprost has been demonstrated across multiple ethnic groups, including African American patients. Latanoprost has also been demonstrated to be effective in lowering eye pressure in a 3 month trial conducted in paediatric patients.

VI.2.3. Unknowns Relating to Treatment Benefits

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

- Pregnant and breastfeeding women;
- Patients with kidney disease; and
- Patients with liver disease

VI.2.4. Summary of Safety Concerns

Table 54. Important Identified Risks

Risk	What is Known	Preventability
Conjunctival hyperaemia	Redness of the eye is a very common possible side effect, likely to affect more than 1 in 10 patients.	This side effect is not preventable. However, the product label warns about the risk of conjunctival hyperaemia associated with latanoprost treatment, and therefore, doctors will be able to counsel patients appropriately regarding this possible common side effect.
Eyelash and vellus hair changes	A very gradual change to the eyelashes and fine hairs around the treated eye, involving an increase in the colour (darkening), length, thickness, and number of eye lashes is a very common possible side effect, likely to affect more than 1 in 10 patients is. This has been mostly reported in Japanese patients.	This side effect is not preventable. However, the product label warns about the risk of eyelash and vellus hair changes associated with latanoprost treatment, and therefore, doctors will be able to counsel patients appropriately regarding this possible common side effect. Also, proper application of the eyedrops (as specified in the patient information leaflet), and wiping any excess eye drop fluid from the skin may reduce the occurrence of vellus hair changes.

Table 54. Important Identified Risks

Risk	What is Known	Preventability
Periorbital skin discolouration	Darkening of the skin of the eyelids is a rare possible side effect, likely to affect less than 1 in every 1000 patients.	This side effect is not preventable. However, the product label warns about the risk of periorbital skin discolouration associated with latanoprost treatment, and therefore, doctors will be able to counsel patients appropriately regarding this possible rare side effect. Also, proper application of the eyedrops (as specified in the patient information leaflet), and wiping any excess eye drop fluid from the skin may reduce the occurrence of periorbital skin discolouration.
Iris hyperpigmentation	A gradual increase in the amount of brown pigment in the coloured part of the eye known as the iris is a very common possible side effect, likely to affect more than 1 in 10 patients is. This change occurs more commonly in mixed-colour eyes than in eyes of one colour.	This side effect is not preventable. However, the product label warns about the risk of iris hyperpigmentation associated with latanoprost treatment, and therefore, doctors will be able to counsel patients appropriately regarding this possible common side effect.
Keratitis herpetic	In rare cases (likely affecting less than 1 in every 1000 patients), patients may develop a viral infection with the herpes simplex virus.	This side effect is not preventable. However, the product label warns about the risk of keratitis herpetic associated with latanoprost treatment, and therefore, doctors will be able to counsel patients appropriately regarding this possible side effect.

Table 55. Important Potential Risks

Risk	What is Known
Cystoid macular oedema	There is a possible risk of patients developing cystoid macular oedema (likely affecting less than 1 in every 100 patients), which is the development of a fluid within the layers of the retina.
Aggravation of asthma	In rare cases (likely affecting less than 1 in every 1000 patients), there is a possible risk of patients experiencing a worsening of asthma.

Table 56. Missing Information

Risk	What is Known
Ocular tolerability in paediatric population	Latanoprost contains the preservative BAK. BAK has been reported to cause damage to the clear surface of the eye (the cornea), may cause eye irritation, and is known to discolour soft contact lenses. Patients who already have medical conditions affecting the cornea may be more susceptible to BAK 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	No studies investigating drug interactions have been conducted in paediatric patients.
Use in pregnant and lactating women	Because latanoprost has not been studied in pregnant or breastfeeding women, there is little information on the risks to pregnant women or their newborns. No potential for reproductive or developmental toxicity has been observed for latanoprost in animal studies.

BAK = benzalkonium chloride.

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 a PIL. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PIL for latanoprost (Xalatan/Latanoprost Pfizer) can be found on the European Public Assessment Report page for Xalatan/Latanoprost Pfizer.

VI.2.6. Planned Post-Authorisation Development Plan

Table 57. List of Studies in Post-Authorisation Development Plan

Study/Activity (Including Study Number)	Objectives	Safety Concerns/ Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
A6111144 Long-term surveillance study to monitor hyperpigmentation changes in the eye in paediatric populations Phase IV	To describe the incidence (proportion and rate) of hyperpigmentation changes in the eye over a total of 10-year follow up period by combining the data collected in the 3-year A6111143 study	Safety: Long-term ocular and systemic safety in the paediatric population	Ongoing FSFV date: 10 March 2014	Projected study report: 2024

Table 57. List of Studies in Post-Authorisation Development Plan

Study/Activity (Including Study Number)	Objectives	Safety Concerns/ Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
	and the subsequent 7-year A6111144 study, among paediatric patients with glaucoma or elevated IOP who have completed the 3-year cohort study (A6111143).			

FSFV = First Subject First Visit; IOP = Intraocular pressure

Studies that are a Condition of the Marketing Authorisation

None of the above studies are conditions of marketing authorisation.

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

Major changes to the RMP over time are shown in Table 58.

Table 58. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	28 Jan 2010	List of important potential risks Cystoid macular oedema Aggravation of asthma	--
1.1	31 Mar 2010	No additional risks added.	Corrections and clarifications to initial version of RMP.
2.0	11 June 2010	Addition of important identified risks category, and updates to important potential risks. Important identified risks added Conjunctival hyperaemia Eyelash and vellus hair changes Periorbital skin discolouration Iris hyperpigmentation Updated list of important potential risks Cystoid macular oedema Aggravation of asthma Ocular and cutaneous melanoma	Addition of information and data in response to regulatory feedback.

Table 58. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
3.0	31 May 2011	Update to identified risk category. Updated list of important identified risks Conjunctival hyperaemia Eyelash and vellus hair changes Periorbital skin discolouration Iris hyperpigmentation Keratitis herpetic Other changes Addition of paediatric indication. Addition of action plans.	Addition of information and data in response to regulatory feedback and PSUR submission.
3.1	18 Dec 2012	Updated to include information on protocol amendment to Study A6111143 (long-term safety study in paediatric patients).	--
4.0	04 February 2014	No changes to identified or potential risks.	Updated to new format based on the EMA Guideline on Good Pharmacovigilance Practices Module V – Risk Management Systems (June 2012)
5.0	02 February 2017	Updated to include information from completed non-interventional PASS A6111143 and A6111157 and proposed removal of ocular and cutaneous melanoma as an important potential risk based on A6111157 study results.	--

EMA = European Medical Association; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan.