VI.2 Elements for a Public Summary

T2345/T2346 is a preservative free eye drop solution that contains the active substance latanoprost.

VI.2.1 Overview of disease epidemiology

T2345/T2346 is used to treat conditions known as open angle glaucoma and ocular hypertension. Both of these conditions are linked with an increase in the pressure within your eye(s), eventually affecting your eye sight.

By the year 2020, it has been estimated that there will be about 59 million people with open angle glaucoma. Risk factors for open-angle glaucoma include increased age, African ethnicity, family history, increased pressure inside the eye, myopia, and decreased corneal thickness (the cornea is the transparent layer in front of the eye that covers the pupil and iris).

Bilateral blindness (blindness in both eyes) from glaucoma has been projected to affect more than 11 million people worldwide by 2020.

T2345/T2346 belongs to a group of medicines known as prostaglandins. It lowers the pressure within your eye by increasing the natural outflow of fluid from inside the eye into the bloodstream.

When intraocular pressure is raised, it causes damage to the retina (the light-sensitive membrane at the back of the eye) and to the optic nerve that sends signals from the eye to the brain. This can result in serious vision loss and even blindness. By lowering the pressure, T2345/T2346 reduces the risk of damage.

The medicine can only be obtained with a prescription.

The dose is one drop of T2345/T2346 in the affected eye(s) once a day, preferably in the evening.

VI.2.2 Summary of treatment benefits

The company provided data from the published literature on Latanoprost Reference Product (XALATAN), already authorised in the European Union (EU).

Moreover, T2345 was evaluated in 462 adults with ocular hypertension or glaucoma. In these studies T2345 was compared with the preserved 0.005% latanoprost reference product (XALATAN).

- LT2345-PII-10/07 – 60 patients – duration 6 weeks
- LT2345-PIII-12/08 – 402 patients – duration 3 months

The main measures of effectiveness were the average reduction in eye pressure. After three months, the efficacy of T2345 was not inferior that of XALATAN.

VI.2.3 Unknowns relating to treatment benefits

Overall, the patients enrolled in clinical trials represent the population that would expect to receive latanoprost, with the exception of children, pregnant women or nursing mothers, patients with advanced glaucoma, patients who have been operated for cataracts, patients with a history of active intraocular inflammation and/or with active intraocular disease.

T2345/T2346 contains macrogolglycerol hydroxystearate (derived from castor oil). No long-term safety data are currently available on this excipient.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reaction (Hypersensitivity)	Allergy induced by topical glaucoma treatment is primarily seen in the conjunctiva and around the eye. Serious allergic reactions to latanoprost are rare.	Yes, by avoiding use of latanoprost in patients with hypersensitivity to latanoprost or to any of the excipients, or with a tendency to develop allergies and asthma. Also by monitoring for early symptoms.
Change in eye colour **Hyperpigmentation (darkening around the eye)**	Iris darkening (frequency ≥1/10) and skin darkening around the eyes (frequency >1/100 to <1/10) have been reported with latanoprost. They do not pose a known threat to vision or health. Skin changes seem to be reversible after discontinuation of the medicine. However, iris darkening is often irreversible.	The risk of iris darkening appears to depend on eye colour before treatment. Patients with non-homogenously blue, grey or hazel irises show greater changes. Caution should be exercised when treating glaucoma only in one eye with prostaglandin analogues (class of medicines to which travoprost belongs).
Hypertrichosis (excessive growth of hair)	Excessive growth of hair is considered as a non-serious and mild effect associated with the use of prostaglandin analogues.	Termination of prostaglandin analogue treatment may reverse this effect 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.
Increased risk of swelling of the retina (macular oedema including cystoid macular oedema)	Macular oedema has been reported during treatment with Latanoprost and other products from the same class. This effect is usually reversible after discontinuation of the medicine.	Yes, by avoiding use of Latanoprost in 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). If Latanoprost is used in such patients, patients

Risk	What is known	Preventability
		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.
Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis)	Symptomatic iritis (inflammation of the iris) appears to be an uncommon adverse event associated with all prostaglandin analogues. Its course is generally mild and the inflammation resolves upon discontinuation of the medicine with or without anti-inflammatory therapy.	Yes, by using Latanoprost with caution in patients with a history of iritis, or with risk factors for iritis. Reinitiating therapy after an episode of iritis may not be advisable.
Increased risk of viral infection of the eye (Herpes simplex virus)	Developing a viral infection of the eye caused by the herpes simplex virus (HSV) has been reported as a possible side-effect with latanoprost	Yes, by using Latanoprost with caution in patients with current or a history of viral infection of the eye caused by the herpes simplex virus (HSV).
Respiratory disorders (affecting the airways)	Respiratory disorders such as dyspnoea (difficulty breathing), asthma and worsening of asthma have been associated with the use of prostaglandin analogues. These and other respiratory symptoms have been reported with the use of Latanoprost.	Yes, by avoiding use of Latanoprost in patients with pre-existing respiratory disorders.
Cardiac disorders	Cardiac disorders such as angina pectoris (pains to the chest, jaw and back), bradycardia (slow heart rate), chest pain have been reported in association with Latanoprost administration although they are considered very rare	Yes, by avoiding use of Latanoprost in patients with pre-existing cardiovascular disorders.

Important Potential Risk

Risk	What is known
Risk of ocular overdose or concomitant use of another prostaglandin	Prostaglandin analogues, when not used adequately, e.g. not exactly as described in the leaflet or as your doctor told you, may have reduced efficacy. For example, a higher daily dosing regimen or the association with another prostaglandin analogue may reduce the efficacy of T2345/T2346.
Use during pregnancy and lactation	Animal studies with latanoprost have shown reproductive toxicity. Pregnant women, women of childbearing potential and breastfeeding women were excluded from participation in clinical trials. Neither T2345 nor T2346 should be used during pregnancy, breastfeeding, or in women of childbearing potential unless they are using adequate contraceptive methods.
Melanoma (pigmented skin cancer)	Prostaglandin analogues are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Melanoma was not seen in the clinical trials for 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.
Vascular disorders (hypertension)	Hypertension (high blood pressure) has been reported in association with Latanoprost administration although they are considered very rare. Vascular disorders such as arterial hypertension (high blood pressure) is not listed in Xalatan SPC up to date. Nevertheless, hypertension is listed in the SPC of other Prostaglandin analogs (e.g. Travoprost) such as Izba/Travatan.

Use for cosmetic purposes as eye lashes enhancer	Excessive growth of hair is considered as a non-serious and mild effect associated with the use of prostaglandin analogues (hypertrichosis). Hypertrichosis refers to an increase in the length, thickness, and/or number of eyelashes. Although this can be desirable from a cosmetic point of view in some patients, unilateral occurrence can be unwanted. It can also influence drop instillation. In some patients, this misuse has been identified in Xalatan or/and in other prostaglandin drugs post-marketing experience.
Use in paediatric population	During the development of T2345/T2346, patients under the age of 18 years have been excluded from participation in clinical trials. Thus, the safety and efficacy of T2345/T2346 in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available. However, recently, the reference product XALATAN, was studied in children and following the evaluation of the results from these clinical studies, the conclusion of the EMA assessment was that the benefit risk balance was in favour of the use of latanoprost 0.005% ophthalmic solution in a paediatric population from 0 to <18years. However, in children from 0 to < 3 years old that mainly suffers from primary congenital glaucoma (PCG), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

Missing information

Risk	**What is known**
Long-term ocular safety (due to the presence of macrogolglycerol hydroxystearate (derived from castor oil)	T2345/T2346 contains macrogolglycerol hydroxystearate (derived from castor oil) which may cause delayed ocular reaction. Therefore, close surveillance of delayed ocular reaction will be performed.

VI.2.5 Summary of risk minimisation measures by safety concern

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

The Summary of Product Characteristics and the Package leaflet for T2345/T2346 can be found in the X's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Study number and title	Objectives	Safety concerns / Efficacy issues addressed	Status	Date for submission of interim or final reports
LT2345-PIV-02/13: Phase IV, international, multicentre, randomised, investigator masked, 3-month duration, 3-parallel group study versus reference products (LUMIGAN 0.01% and LUMIGAN 0.03% UD) in which 360 evaluable patients are planned.	To assess the safety and the efficacy of MONOPROST in comparaison with LUMIGAN 0.01% and LUMIGAN 0.03% UD in patients with primary open angle glaucoma or ocular hypertension initially treated, stabilized by monotherapy of LUMIGAN 0.01% with ocular signs and symptoms of intolerance to previous eye drops	Safety and Efficacy	Ongoing started December 2013 Planned completion of clinical phase: July 2016	Date for submission of final report not yet specified
LT2345-PIV-05/13 Phase IV, multicenter, randomised, open label, 3-month duration, 2-parallel group study versus reference product (XALATAN) in which 300 evaluable patients are planned.	To assess the safety and the efficacy of MONOPROST in comparison with XALATAN in patients with primary open angle glaucoma or ocular hypertension initially treated, stabilized by monotherapy of XALATAN since at least 6 months.	Safety and Efficacy	Clinical phase completed	Date for submission of final report not yet specified

Studies which are a condition of the marketing authorisation

The above study was not a condition of the marketing authorisation for T2345/T2346.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
01	08 Nov. 2013	• Allergic reaction (Hypersensitivity) • Change in eye colour • Increased risk of swelling of the	First version of the RMP

Version	Date	Safety Concerns	Comment
		retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Use in paediatrics • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	
02	20 Dec. 2013	• Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Use in paediatrics • Long term safety of macrogolglycerol hydroxystearate (derived from	Addition of the data concerning the multidose preservative-free bottle presentation and harmonisation with a competitor

Version	Date	Safety Concerns	Comment
		castor oil)	
2.1	12 Mar. 2015	Identified Risks • Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders Potential Risks • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Use in paediatrics • Use for cosmetic purposes as eye lashes enhancer (hypertrichosis) Missing information • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	Update in the context of variation FR/H/0499/001/II/006 for T2345
03	24 Aug. 2015	Identified Risks • Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the	Update in the context of MA procedure FR/H/499/002/DC (answers to questions at D106) for T2346 and inclusion of post marketing experience for T2345 (version submitted

Version	Date	Safety Concerns	Comment
		retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders Potential Risks • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Hypertension • Use in paediatrics • Use for cosmetic purposes as eye lashes enhancer (hypertrichosis) Missing information • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	only to the RMS France in the draft D106 response document for FR/H/0499/002/DC)
3.1	10 June 2016	Identified Risks • Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders	Minor modifications (delete of “airless”) in the context of MA procedure FR/H/499/002/DC at D106 for T2346 (version submitted to all Members States included in FR/H/0499/002/DC at D106)

Version	Date	Safety Concerns	Comment
		Potential Risks • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Hypertension • Use in paediatrics • Use for cosmetic purposes as eye lashes enhancer (hypertrichosis) Missing information • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	
3.2	22 August 2016	Identified Risks • Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders Potential Risks • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Hypertension • Use in paediatrics	Minor Update in the context of MA procedure FR/H/499/002/DC (answers to questions at D120 and D145)

Version	Date	Safety Concerns	Comment
		• Use for cosmetic purposes as eye lashes enhancer (hypertrichosis) Missing information • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	
3.3	30 September 2016	Identified Risks • Allergic reaction (Hypersensitivity) • Change in eye colour • Hyperpigmentation (darkening around the eye) • Hypertrichosis (excessive growth of hair) • Increased risk of swelling of the retina (macular oedema including cystoid macular oedema) • Increased risk of inflammation of the iris, the coloured part of the eye (iritis/uveitis) • Increased risk of viral infection of the eye (Herpes simplex virus) • Severe asthma or not-controlled asthma • Cardiac disorders Potential Risks • Risk of ocular overdose or concomitant use of another prostaglandin • Use in Pregnant or breast feeding women • Melanoma • Hypertension • Use in paediatrics • Use for cosmetic purposes as eye lashes enhancer (hypertrichosis) Missing information • Long term safety of macrogolglycerol hydroxystearate (derived from castor oil)	Change of proposed SmPC for T2346 (version 08) in the context of MA procedure FR/H/499/002/DC (D195)