VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Studies estimated that 3-6 million people in the United States alone, including 4-10% of the population older than 40 years, have intraocular pressures of 21 mm Hg or higher, without detectable signs of glaucomatous damage using current tests.
Ocular hypertension is 10-15 times more likely to occur than primary open-angle glaucoma, a common form of glaucoma. That means that out of every 100 people older than 40 years about 10 will have pressures higher than 21 mm Hg, but only 1 of those people will have glaucoma. In approximately 3% of people with ocular hypertension, could lead to vision loss.

Some studies have found that the average intraocular pressure in blacks is higher than in whites. In addition, average intraocular pressure in women (especially after menopause) is higher than in men.
Studies also show that men with ocular hypertension may be at a higher risk for glaucomatous damage.

Glaucoma is the second leading cause of blindness in the world (after cataracts) and the leading cause of blindness among African-Americans. **Open-angle glaucoma** is the most common type of glaucoma among populations of European or African descent, whereas angle-closure glaucoma is more common among populations of Asian descent. It is estimated that there are 44.7 million people with open-angle glaucoma worldwide in 2010, and that this number will increase to 58.6 million in 2020. It is estimated that there are 2.8 million people with open-angle glaucoma in the United States in 2010, and that the number will increase to 3.4 million in 2020.
The Barbados Eye Study found ocular hypertension present more frequently in women. Mean intraoccular pressure slowly rises with increasing age. Age older than 40 years is considered a risk factor for the development of ocular hypertension and primary open-angle glaucoma. Black subjects had almost 3 times the age-adjusted prevalence of glaucoma than white subjects.

VI.2.2 Summary of treatment benefits

Travoprost is a highly potent and efficacious compound for lowering intraocular pressure as both a monotherapy agent as well as in combination with other drugs. Additional efficacy in African Americans is a particularly important benefit since this group of patients often demonstrates the most advanced, aggressive form of disease.
The majority of the randomized controlled trials have found travoprost to be equally efficacious in comparison with latanoprost and bimatoprost in eyes with ocular hypertension and primary open angle glaucoma.
Recent trials have suggested that travoprost has a robust effect in lowering of intraocular pressure with little diurnal fluctuation, which can last beyond the standard dosing interval of 24 hours. Other pilot trials suggested that the travoprost effect can continue up to 84 hours after the final dose.
Despite the development of minor adverse effects, such as conjunctival hyperemia, iris and eyelid hyperpigmentation, eyelash changes, and other rare cases of iritis and macular edema, which are

common to prostaglandin's therapy (latanoprost, travoprost, tafluprost, bimatoprost, or isopropyl unoprostone), the efficiency and safety of travoprost have been extensively demonstrated.

VI.2.3 Unknowns relating to treatment benefits

In the SmPC of *'[Travoprost] 30µg/mL, eye drops, solution'* is stated that efficacy of the product in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

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

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Blurred, reduced or abnormal vision *(Macular oedema)*	The macula is a very small area at the center of the retina - a thin layer of light-sensitive tissue that lines the back of the eye. Light rays are focused onto the retina, where they are transmitted to the brain and interpreted as the images seen. It is the macula that is responsible for pinpoint vision, allowing reading, sewing or recognizing a face. Macular edema develops when blood vessels in the retina are leaking fluids. The macula does not function properly when it is swollen. Vision loss may be mild to severe, but in many cases, peripheral (side) vision remains	Yes, by avoiding use of travoprost 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 travoprost 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.
Change in the colour of iris	Travoprost may gradually	The risk of iris darkening

(the coloured part of the eye) *(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.	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). These changes are solely cosmetic in nature, and have not posed a health risk in any form. However, an ophthalmologist should be advised
Increase of the length, thickness, colour and/or number of the eyelashes that may cause unusual hair growth on the eyelids *(Hypertrichosis)*	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.	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. These changes are solely cosmetic in nature. However, an ophthalmologist should be advised
Pain, sensitivity to light, blurred vision, and redness *(Iris and uveal inflammation)*	Uveitis and iritis are known adverse effects of travoprost (prostaglandin F2 analogues adverse event) and are most common with latanoprost. Iritis is a serious condition that, if left untreated, could lead to glaucoma or blindness.	Drug-induced uveitis is almost always reversible within weeks of discontinuation of the drug and treatment of the inflammation with topical corticosteroid. An ophthalmologist should immediately be advised.
Increased or decreased blood pressure, irregular, increased, or decreased heart rate	Cardiac and vascular disorders are adverse event related to systemic absorption of the	Yes, by using travoprost with caution in patients with a history of iritis, or with risk

(bradycardia) *(Cardiac and vascular disorders)*	drug. These adverse events may occurred uncommonly (may affect up to 1 in 100 people). These effects should be considered in elderly and in patients with cardiac, respiratory or neurological disease	factors for iritis. Reinitiating therapy after an episode of iritis may not be advisable. Consultation of a doctor is advised.
Breathlessness or wheezing or increase of asthma symptoms *(Respiratory disorders)*	Respiratory disorders are adverse event related to systemic absorption of the drug that occurs rarely. However, topical applied travoprost should be avoided in patients with severe corticodependent asthma	Yes, by discontinuation of the treatment in patients with pre-existing respiratory disordersand immediate consultation of a doctor
Allergy *(Hypersensitivity reactions)*	Allergy induced by topical glaucoma treatment is primarily seen in the conjunctiva and around the eye. Serious allergic reactions to travoprost are rare.	Yes, by avoiding use of travoprost in patients with hypersensitivity to travoprost or to any of the excipients, or with a tendency to develop allergies and asthma. Also by monitoring for early symptoms.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Corneal damage due to long term use of preserved eye drops	Travoprost eye drops solution is indicated to decrease elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. This is a long-term condition where patients are usually exposed to topical medications for life. The presence of a preservative increases the risk of adverse effects on the corneal surface (cell loss and tear film disruption) and the possibility of hypersensitivity reactions. The damage depends on the agent, the posology and the length of treatment. Clinical trials involving the originator product Travatan with a duration of up to 5 years as well as postmarketing experience with Travatan have not confirmed an increased frequency of corneal events. Therefore, this is considered only as a potential risk for [Travoprost].
Melanoma	Prostaglandin analogues are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Melanoma was not seen in the clinical trials for

	travoprost which studied 6,385 patients and healthy volunteers. Three spontaneous cases of melanoma have been reported to date, two with travoprost and one with the fixed combination of travoprost and timolol. Four cases have been reported in the literature with members of the same pharmaceutical class: one eyelid melanoma associated with bimatoprost (another type of prostaglandin analogue) and one choroidal melanoma and two cutaneous melanomas associated with latanoprost (another type of prostaglandin analogue). However, a direct link between prostaglandin analogue use and development of melanoma has never been documented.
Use during pregnancy and lactation	Animal studies with travoprost have shown reproductive toxicity. Pregnant women, women of childbearing potential and breastfeeding women were excluded from participation in clinical trials. 17 spontaneous cases reporting exposure during pregnancy with associated adverse events have been received. [Travoprost] should be used during pregnancy, breastfeeding, or in women of childbearing potential unless they are using adequate contraceptive methods.

Missing information	
Risk	**What is known**
Use in paediatric population	<u>Paediatric population</u> Travoprost 30 µg/mL has not been specifically studied in a clinical trial involving paediatric subjects. However, a modelling approach demonstrated that IOP lowering would be expected to be equivalent in paediatric patients aged 3 years and above using both travoprost 30 µg/mL and travoprost 40 µg/mL eye drops, solution. The studies used in the model were two dose response trials, one Phase III study using travoprost 30 µg/mL and a paediatric study using travoprost 40 µg/mL eye drops, solution. The efficacy of travoprost 40 µg/mL eye drops, solution in paediatric patients from 2 months to less than 18 years of age was demonstrated in a 12-week, double-masked clinical study of travoprost compared with timolol in 152 patients diagnosed with ocular hypertension or paediatric glaucoma. Patients received either travoprost 0.004% once daily or timolol 0.5% (or 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the intraocular pressure (IOP) change from baseline at Week 12 of the study. Mean IOP reductions in the travoprost and timolol groups were similar (see Table 4). In the age groups 3 to < 12 years (n=36) and 12 to <18 years (n=26), mean IOP reduction at Week 12 in the travoprost group was similar to that in the timolol group. Mean IOP reduction at Week 12 in the 2 months to < 3 years of age group was 1.8 mmHg in the travoprost

	group and 7.3 mmHg in the timolol group. IOP reductions for this group were based on only 6 patients in the timolol group and 9 patients in the travoprost group where 4 patients in the travoprost group versus 0 patients in the timolol group had no relevant mean IOP reduction at Week 12. No data are available for children less than 2 months old. The effect on IOP was seen after the second week of treatment and was consistently maintained throughout the 12 week period of study for all age groups. The safety and efficacy of travoprost 30 µg/mL in children below the age of 3 years hasve not been established. No recommendation on a posology below the age of 3 years can be made.
Potential interactions	No specific pharmacokinetic drug-drug interactions are known for travoprost. Interaction studies with other medicinal products and other forms of interation have not been performed.

VI.2.5 Summary of risk minimisation measures by safety concern

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

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	23.07.2016	**Important identified risks** • Macular oedema • Hyperpigmentation • Hypertrichosis • Iris and uveal inflammation • Cardiac and vascular disorders	Initial version

		• Respiratory disorders • Hypersensitivity **Important potential risks** • Melanoma • Corneal damage due to use of preserved eye drops • Use during pregnancy and lactation **Missing information** • Use in paediatric population • Potential interactions	
1.0	28.02.2017	**Importan identified risks** • Macular oedema • Hyperpigmentation • Hypertrichosis • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions **Important potential risks** • Melanoma • Corneal damage due to use of preserved eye drops • Use during pregnancy and lactation **Missing information** • Use in paediatric population • Potential interactions	RMP update in response to day70 RMS Asssessment report
1.0	20.07.2017	**Missing information** • **Use in children below the age of 3 years**	RMP update in response to day160 RMS Asssessment report. Updated PIL and SmPC
1.0	04.09.2017		Updated PIL and SmPC