VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The term **ocular hypertension** usually refers to any situation in which the pressure inside the eye, called intraocular pressure, is higher than normal. Eye pressure is measured in millimeters of mercury (mm Hg). Normal eye pressure ranges from 10-21 mm Hg. Ocular hypertension is an eye pressure of greater than 21 mm Hg. Ocular hypertension should not be considered a disease by itself. Instead, ocular hypertension is a term that is used to describe individuals who should be observed more closely than the general population for the onset of glaucoma. Studies estimated that 3-6 million people in the United States alone, including 4-10% of the population older than 40 years, have intraocular pressures of 21 mm Hg or higher, without detectable signs of glaucomatous damage using current tests. Some studies have found that the average intraocular pressure in blacks is higher than in whites. In addition, average intraocular pressure in women (especially after menopause) is higher than in men.

The worldwide frequency of glaucoma is increasing. **Glaucoma** is a leading cause of irreversible bli ndness with 60 million cases worldwide and 2.2 million in the United States. Early diagnosis and tre atment is critical to managing glaucoma. **Open-angle glaucoma** is the most common type of glauco ma among populations of European or African descent. If untreated, the disease can lead to blindnes s. In fact, 11.2 million people are predicted to go blind from glaucoma by the year 2020, due in part t o lack of access to medical treatments and providers.

Primary congenital glaucoma occurs in 1 out of every 10,000 births in the U.S. Primary congenital g laucoma accounts for approximately 50% to 70% of all cases of congenital glaucoma. Most cases of pediatric glaucoma are diagnosed by the age of six months, with 80% diagnosed by the first year of l ife. In diagnosed cases, about 2/3 of the patients are male. In about 3/4 of all cases, the glaucoma aff ects both eyes (bilateral).

VI.2.2 Summary of treatment benefits

Travoprost is a highly potent and efficacious compound for lowering intraocular pressure as both a monotherapy agent as well as in combination with other drugs. Additional efficacy in African Americans is a particularly important benefit since this group of patients often demonstrates the most advanced, aggressive form of disease.

The majority of the randomized controlled trials have found travoprost to be equally efficacious in comparison with latanoprost and bimatoprost in eyes with ocular hypertension and primary open angle glaucoma.

Recent trials have suggested that travoprost has a robust effect in lowering of intraocular pressure with little diurnal fluctuation, which can last beyond the standard dosing interval of 24 hours. Other pilot trials suggested that the travoprost effect can continue up to 84 hours after the final dose.

[Travoprost] preservative-free eye drops solution does not contain benzalkonium chloride, a preservative used to curb microbial activity. Exposure to preservatives is a major reason for the

development of adverse effects as they have a potential to cause toxicity to the ocular surface, especially in the long-term therapies.

Despite the development of minor adverse effects, such as conjunctival hyperemia, iris and eyelid hyperpigmentation, eyelash changes, and other rare cases of iritis and macular edema, which are common to prostaglandin's therapy (latanoprost, travoprost, tafluprost, bimatoprost, or isopropyl unoprostone), the efficiency and safety of travoprost, have been extensively demonstrated.

VI.2.3 Unknowns relating to treatment benefits

In the SmPC of *'[Travoprost] preservative-free 40µg/mL, eye drops, solution'* is stated that travoprost can be used in paediatric patients from 2 months to < 18 years at the same posology as in adults. However, data in the age group 2 months to < 3 years (9 patients) is limited. No data are available for children below the age of 2 months. No long-term safety data are available in the paediatric population.

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

There are no data on the effects of travoprost on human fertility.

VI.2.4 Summary of safety concerns

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 discontinuation of the treatment and consultation of an ophthalmologist.

Change in the colour of iris (the coloured part of the eye) *(Hyperpigmentation)*	Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes.	These changes are solely cosmetic in nature, and have not posed a health risk in any form. However, an ophthalmologist should be advised.
Increase of the length, thickness, colour and/or number of the eyelashes that may cause unusual hair growth on the eyelids *(Hypertrichoses)*	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. This side-effect does not have particularly deleterious pshysicological effects on the patients.	These changes are solely cosmetic in nature. However, an ophthalmologist should be advised.
Pain, sensitivity to light, blurred vision, and redness *(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 (bradycardia) *(Cardiac and vascular disorders)*	Cardiac and vascular disorders are adverse event related to systemic absorption of the drug. These adverse events may occurred uncommonly (may affect up to 1 in 100 people). These effects should be considered in elderly and in patients with cardiac, respiratory or neurological disease.	Yes, by consultation of a doctor.
Breathlessness or wheezing or increase of asthma symptoms *(Respiratory disorders)*	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 and immediate consultation of a doctor.
Oversensitivity reactions *(Hypersensitivity reactions)*	Allergic reaction such as swelling be neath the skin that can occur in areas such as the face and limbs, and can o bstruct the airway which may cause d ifficulty swallowing or breathing, hiv es or itchy rash, localized and genera lized rash, itchiness may occur.	Treatment should be discontinued immediately after apparition of an allergic symptom. Patient should ask physician advice.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Ocular and skin melanomas	Prostaglandin analogues are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Melanoma was not seen in the clinical trials for travoprost which studied 6,385 patients and healthy volunteers. 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	In ocular toxicity studies in monkeys, administration of Travoprost at a dose of 0.45 microgram, twice a day, was shown to induce increased palpebral fissure. Topical ocular administration of Travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of Travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^{3}H-Travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml). Travoprost must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place. In addition, Travoprost should not be used during pregnancy unless clearly necessary neither in breast-feeding mothers. In case that any of the product comes into contact with the skin then it should be washed off straight away.

Missing information	
Risk	**What is known**
Long term safety in the paediatric population	Paediatric population Efficacy and safety data in the age group 2 months to < 3 years (9 patients) is limited (see section 5.1). No data are available for children below the age of 2 months. In children < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment. No long-term safety data are available in the paediatric population. 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.
Potential interactions	Interaction studies with other medicinal products and other forms of interation have not been performed.

VI.2.5 Summary of risk minimisation measures by safety concern

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

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

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

Version	Date	Safety concerns	Change
1.0	25.09.2015	**Important identified risks**	Initial version

		• Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information** • Potential interactions	
1.0	11.05.2016	**Important identified risks** • Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information** • Long term safety in paediatric population • Potential interactions	Implementation of day 70 and day 100 assessor's comments
1.0	30.08.2016	**Important identified risks** • Macular oedema	Implementation of day 120 assessor's comments

		• Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information** • Long term safety in paediatric population • Potential interactions	
1.0	20.10.2016	**Important identified risks** • Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information**	Alignment with the a greed wording of the Product Information

		• Long term safety in paediatric population • Potential interactions	