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

Drugs to treat glaucoma are classified by their active ingredient. These include: prostaglandin analogs, beta blockers, alpha agonists, carbonic anhydrase inhibitors and combination drugs like travoprost/timolol.

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.

Beta blockers such as timolol are the second most often used class of medication and work by decreasing production of fluid from the eye. They have systemic side effects that can be minimized by closing the eyes following application or using a technique called punctual occlusion that prevents the drug from entering the tear drainage duct and systemic circulation.

There are many studies comparing safety and efficacy of timolol maleate with other drugs using to treat glaucoma. Timolol has been shown safe and effective alone or in combination formulations.

VI.2.3 Unknowns relating to treatment benefits

In the SmPC of *'[Travoprost+ Timolol] 40µg/mL + 5mg/mL, preservative free 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		
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	You should advise with an ophthalmologist however these changes are solely cosmetic in nature, and

	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.	have not posed a health risk in any form.
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.	You should advise with an ophthalmologist however, these changes are solely cosmetic in nature.
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. Travoprost/timolol should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.	Yes, by discontinuation of the treatment and immediate consultation of a doctor.
Irritation of the eye - dry eyes *(Corneal toxicity – dry eye*	Signs and symptoms of eye irritation (e.g. burning, stinging, itching, tearing, redness), inflammation of the eyelid, inflammation in the cornea, blurred vision, decreased corneal sensitivity, dry eyes, corneal erosion (damage to the front layer of the eyeball), drooping of the upper eyelid (making the eye stay half closed) double vision,	Yes, by informing your ophthalmologist in case of appearance of such symptoms. Your doctor should monitor you for local and systemic adverse effects.

	sensitivity to light, discharge from the eye, pain in the eye, have been reported.	

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Ocular and skin melanomas	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, as well as form moles. Ocular melanoma accounts for approximately 5-12% of all melanoma cases. Some studies suggest that fair skin type is a risk factor for ocular melanoma.
Use during pregnancy and lactation	*Travoprost* Topical ocular administration of travoprost to monkeys, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. 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. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml). *Timolol* Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).

Missing information	
Risk	**What is known**
Potential interactions	Interaction studies with other medicinal products and other forms of interation have not been performed.
Exposure in paediatric population	The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have not been established. No data are available

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	26.09.2016	**Important identified risks** • Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye **Important potential risks** • Ocular and skin melanomas • Use during pregnancy and lactation **Missing information** • Potential interactions • Exposure in paediatric population	Initial version
1.0	06.06.2017	**Important identified risks** • **Macular oedema** • **Hyperpigmentation** • **Hypertrichoses** • **Iris and uveal inflammation** • **Cardiac and vascular disorders** • **Respiratory disorders** • **Corneal toxicity – dry eye** **Important potential risks** • **Ocular and skin melanomas** • **Use during pregnancy and lactation** **Missing information**	Day 106 responses: change of contact person for this RMP, updated Annex 2 of RMP in accordance to updated proposed SmPC/PIL (no changes introduced with regards to the summary of safety concerns).

		• **Potential interactions** • **Exposure in paediatric population**	
1.0	19.10.2017		Day 160, RMP-PIL updated in accordance to the assessor’s comments