Fredomat 40 µg/ml eye drops, solution

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PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Glaucoma causes irreversible defects in the visual field. This optic neuropathy is progressive and, if left untreated, results in absolute blindness. It is a leading cause of blindness world-wide, affecting 2% of individuals of European descent (8). Glaucoma accounts for 20.5 % of causes of blindness in Europe. 25 million European persons are affected by glaucoma. It has been estimated that 21.8 % of European adults (including 18% of those over 50 years of age) have been diagnosed with glaucoma. According to recent epidemiological studies, Germany (14 %) shows the highest prevalence of glaucoma in Europe followed by the European North of Russia (11.9 %). The lowest prevalence of any type of glaucoma has been registered in France (3.4 %) and the UK (3.3 %). A Spanish epidemiological study showed that primary open-angle glaucoma (2.1 %) was more prevalent in men (2.4 %) than in women (1.7 %) (16). Strong and consistent evidence regarding the risk of developing glaucoma was found for elevated intraocular pressure (IOP), advancing age, non-Caucasian ethnicity and family history of glaucoma. The same applies for greater cup-to-disk ratio and thinner central corneal measurement. There is moderate evidence of an association between glaucoma and migraine, eye injury, myopia and long-term use of corticosteroids, respectively. There is conflicting evidence for high blood pressure, diabetes and smoking (8, 9, 17, 21).

VI.2.2 Summary of treatment benefits

Glaucoma cannot be cured and damage caused by the disease cannot be reversed (6). However, adequate treatment can protect subjects at high risk of the disease or patients with early signs of glaucoma from severe visual impairment and blindness. The assessment that elevated intraocular pressure (IOP) is a major risk factor for glaucoma development is corroborated by controlled clinical trials in which substantial benefit of IOP-lowering treatment for patients suspected to have glaucoma was reported before initial damage was seen (4, 12, 17).

Three studies have been performed which assessed the IOP lowering efficacy of travoprost. In these studies, patients with open-angle glaucoma (OAG) or ocular hypertension who took travoprost 40 microgram/ml experienced 7-8 mmHg (millimetres of mercury, a measurement of pressure) decreases in IOP. The results have been consistent in all three monotherapy pivotal trials. Travoprost 0.004% dosed once daily produced both clinically relevant and statistically significant IOP reductions when used as a monotherapy. The IOP reductions were maintained over the entire 6 to 12 month treatment period (7).

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy in inflammatory ocular conditions, in neovascular, angle-closure, narrow-angle or congenital glaucoma have not been studied. The safety and efficacy in paediatric patients has not yet been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Build-up of fluid in the area of the retina that is responsible for sharp vision (Macular oedema)	Build-up of fluid in the area of the retina that is responsible for sharp vision has been reported in patients using travoprost. Nine cases have been reported for the reference product Travatan®. Considering the number of cases reported and the fact that macular oedema had also been reported with other drugs of the same therapeutic class, the Committee for Medicinal Products for Human Use (CHMP) requested this reaction to be added to section 4.8 of the SmPC (7).	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.
Darkening of eye colour or of skin around the eye (Hyperpigmentation)	Iris darkening (frequency ≥1/10) and skin darkening around the eyes (frequency >1/100 to <1/10) have been reported with travoprost. 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).

Risk	What is known	Preventability
Excessive growth of hair (Hypertrichosis)	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.
Inflammation of certain parts of the eye (Iris and uveal inflammations)	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 travoprost 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.
Risk for the heart and blood vessels (Cardiac and vascular disorders)	Cardiovascular disorders such as angina pectoris (pains to the chest, jaw and back), bradycardia (slow heart rate), chest pain, hypertension and hypotension (high or low blood pressure) have been reported in association with travoprost administration although they are considered very uncommon.	Yes, by avoiding use of travoprost in patients with pre-existing cardiovascular disorders.
Risks for the airways (Respiratory disorders)	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 travoprost.	Yes, by avoiding use of travoprost in patients with pre-existing respiratory disorders.
Allergy (Hypersensitivity)	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)
Pigmented skin cancer (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. 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.
Corneal damage due to use of preserved eye drops	The product 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 travaprost 40 microgram/ml with a duration of up to 5 years as well as postmarketing experience with travaprost 40 microgram/ml have not confirmed an increased frequency of corneal events. Therefore, this is considered only as a potential risk for Travoprost 40 µg/ml eye drops, solution.
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. Travoprost 40 µg/ml eye drops, solution should not 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	During the development of travoprost, patients under the age of 18 years have been excluded from participation in clinical trials. Thus, the safety and efficacy of travoprost 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. Currently 2 clinical trials are ongoing involving paediatric glaucoma patients.
Potential interactions	No specific pharmacokinetic drug-drug interactions are known for travoprost. Interaction studies have not been performed for Travoprost 40 µg/ml eye drops, solution.

VI.2.5 Summary of additional risk minimisation measures by safety concern

NA

VI.2.6 Planned post authorisation development plan

NA

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

NA