VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Glaucoma (eye disease) is a condition which can affect sight, usually due to buildup of pressure within the eye. If left untreated it can result in blindness. It is a leading cause of blindness worldwide. In 2013, the total number of people (aged 40-80 years) with glaucoma was estimated to be 64.3 million (2).

Recent studies have also concluded there are around 6.77 million people (aged 40-80) in Europe alone with glaucoma. Projections for the years 2020 and 2040 indicate there will be 7.12 and 7.85 people (aged 40-80 years) in Europe alone with glaucoma. Studies also show that men are more likely to develop glaucoma than women (2).

Risk factors for glaucoma include increased eye pressure, advancing age, non-Caucasian ethnicity and family history of glaucoma. The most common forms of glaucoma are age-related. If detected early enough, disease progression can be slowed with drug and/or surgical treatment (1).

VI.2.2 Summary of treatment benefits

Glaucoma cannot be cured and damage caused by the disease cannot be reversed (15). 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 increased eye pressure is a major risk factor for glaucoma development is validated by controlled clinical trials in which substantial benefit of eye pressure-lowering treatment for patients suspected to have glaucoma was reported before initial damage was seen (3, 18, 19).

Three studies have been performed which assessed the eye-pressure-lowering-efficacy of travoprost/timolol. In these studies, patients with open-angle glaucoma (type of glaucoma where the pressure in the eye slowly rises and the cornea adapts without swelling) or ocular hypertension (elevated eye pressure) who took travoprost/timolol between 3 and 12 months experienced decreases in eye pressure (17).

These studies were conducted for DuoTrav by Alcon Laboratories Ltd and not by Mylan.

VI.2.3 Unknowns relating to treatment benefits

There is no experience of travoprost/timolol in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma. 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)	Eye swelling due to build-up of fluid in the area of the retina that is responsible for sharp vision has been reported in patients using travoprost/timolol.	By providing adequate information to prescribers and patients in the product labelling
Hyperpigmentation	Travoprost/timolol may change the colour of the iris (the coloured part of the eye). This change may be permanent.	By providing adequate information to prescribers and patients in the product labelling
Hypertrichoses	Travoprost/timolol may change the	By providing adequate information to prescribers and patients in the product labelling
Iris and uveal disorders	Travoprost/timolol may change the colour of the iris (the coloured part of the eye) and may cause blurred vision, abnormal vision, iris inflammation, eye inflammation, sensitivity to light, reduced vision or broken blood vessel in the eye.	By providing adequate information to prescribers and patients in the product labelling
Cardiac and vascular disorders	Travoprost/timolol may cause increased or decreased blood pressure, shortness of breath, decreased heart rate irregular heart rate, heart failure, chest pain, stroke, fainting, increased	By providing adequate information to prescribers and patients in the product labelling

	heart rate, palpitations, slow heart rate, palpitations, oedema (fluid build-up), changes in the rhythm or speed of the heartbeat, congestive heart failure (heart disease with shortness of breath and swelling of the feet and legs due to fluid build-up), a type of heart rhythm disorder, heart attack low blood pressure, Raynaud's phenomenon, cold hands and feet, reduced blood supply to the brain.	
Respiratory disorders	Travoprost/timolol may cause shortness of breath, difficulty breathing, cough, throat irritation, discomfort inside of nose or asthma.	By providing adequate information to prescribers and patients in the product labelling

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Ocular and skin melanoma	Because travoprost/timolol may permanently change the colour of the iris (the coloured part of the eye) and/or of the surrounding skin, by increasing the number of melanosomes (pigment granules) in melanocytes (cells that give the iris colour), before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour and that the long-term effects on the eye and surrounding skin and eyelids are currently unknown. This risk can be mitigated by providing adequate information to prescribers and patients in the product labelling.

Risk	What is known (Including reason why it is considered a potential risk)
Corneal damage due to long-term use of preserved eye drops	Corneal damage may occur during treatment with travoprost/timolol due to the presence of preservative benzalkonium chloride. In order to prevent this, other substances have been developed and are currently undergoing pre-clinical trials, such as travoprost/timolol preserved with polyquaternium-1, for which it has been observed that it induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride. This risk can be mitigated by providing adequate information to prescribers and patients in the product labelling.
Use during pregnancy and lactation	Travoprost/timolol should not be used during pregnancy and lactation as it may negatively affect the foetus. Patients should inform their doctor if they are planning to become pregnant or if they get pregnant during treatment. Pregnant patients should be made aware that travoprost may be absorbed through the skin so they avoid this from happening. This risk can be mitigated by providing adequate information to prescribers and patients in the product labelling.

Missing information

Risk	What is known
Potential interactions	travoprost/timolol may interact with other drugs such as drugs used to induce anaesthesia or drugs used in treatment of hypertension, arrhythmias or other heart disorders, such as oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmic drugs (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine. In patients taking clonidine for hypertension, blood pressure can increase dramatically when clonidine treatment is ceased. Patients taking treatment for arrhythmias or depression may experience increased side effects of the latter due to drug interactions

Risk	What is known
	between them and travoprost/timolol. In order to minimize the risk of occurrence of adverse events due to drug interactions, patients are advised to inform the prescriber if they suffer from any disease or take any kind of treatment. This risk can be mitigated by providing adequate information to prescribers and patients in the product labelling.
Safety and efficacy in children	The safety and efficacy of travoprost/timolol in children and adolescents below the age of 18 years have not been established. No data is available.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. 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

No studies planned.

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

Not applicable.