VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 OVERVIEW OF DISEASE EPIDEMIOLOGY

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, vision loss can result.

Between 3 and 6 million people are at risk for developing Primary Open Angle Glaucoma (POAG) due to elevated intraocular pressure (IOP).

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 a group of eye diseases traditionally characterized by elevated intraocular pressure (IO P). **Open-angle glaucoma** is the most common type of glaucoma among populations of European o r African descent, whereas angle-closure glaucoma is more common among populations of Asian de scent. It is the second leading cause of blindness in the world (after cataracts) and the leading cause of blindness among African-Americans if left untreated.
Glaucoma affects one in 200 people aged 50 and younger, and one in 10 over the age of 80. The Wo rld Health Organization estimated that in 2010 glaucoma accounted for 2% of visual impairment and 8% of global blindness. If the condition is detected early enough, it is possible to arrest the develop ment or slow the progression with medical and surgical means.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

[Bimatoprost/timolol] contains two different active substances (bimatoprost and timolol) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, a prostaglandin analogue. Timolol belongs to a group of medicines called beta-blockers. [Bimatoprost/timolol] is prescribed in adult patients with open-angle glaucoma or ocular hypertension when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.

The majority of patients with glaucoma or ocular hypertension eventually require adjunctive therapy to control their IOP. [Bimatoprost/timolol] combines two active substances in a single formulation for the reduction of IOP by the differential mechanisms of action and complementary pharmacology of the active ingredients. The fixed combination may lead to increased compliance since it is administered more conveniently than the individual products administered adjunctively.

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

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. Therefore, its use is not recommended in these patients.

In addition, bimatoprost/timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

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**
Change in the colour of iris (the coloured part of the eye) *(Iris hyperpigmentation)*	Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iris pigmentation are not known.	Treatment with the lowest therapeutically effective dose and for the shortest recommended period. Patients should consult an ophthalmologist however, these changes are solely cosmetic in nature, and have not posed a health risk in any form.
Damage to the cornea *(Punctate keratitis)*	Superficial punctate keratitis is an eye disorder caused by death of small groups of cells on the surface of the cornea (the clear layer in front of the iris and pupil). Damage to the cornea called “punctuate keratitis” may affect up to 1 in 10 people treated with bimatoprost/timolol.	Patients can usually carry on taking the drops, unless the effects are serious. If patients are worried, they should talk to a doctor or pharmacist. Monitoring of patients is required with frequent of prolonged use specifically in patients with dry eyes or where the cornea is compromised.
(Cystoid 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. 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.	You should tell your doctor if you have now or have had in the past swelling of the retina within the eye leading to worsening vision (known risk factors for macular oedema), for example, cataract surgery.

Asthma and asthma symptoms *(Acute asthma and asthmatic symptoms)*	Asthma is a chronic disease of the airways that makes breathing difficult. With asthma, there is inflammation of the air passages that results in a temporary narrowing of the airways that carry oxygen to the lungs. This results in asthma symptoms, including coughing, wheezing, shortness of breath, and chest tightness. If it is severe, asthma can result in decreased activity and inability to talk. It is not known how common is for patients to develop asthma while on treatment with bimatoprost/timolol.	You should not use this medicine if you have now or have had in past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough). You should talk to your doctor before using this medicine if you have now or have had in the past breathing problems, asthma or chronic obstructive pulmonary disease.
Slow heart beat *(Bradycardia*)	Bradycardia is a slow or irregular heart rhythm, usually fewer than 60 beats per minute. At this rate, the heart is not able to pump enough oxygen-rich blood to your body during normal activity or exercise. As a result, you may feel dizzy or have chronic lack of energy, shortness of breath, or even fainting spells.	You should not use this medicine if you have heart problems such as low heart rate, heart block, or heart failure. You should talk to your doctor before using this medicine if you have now or have had in the past disturbances of heart rate such as slow heart beat.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Cardiovascular events (angina, hypotension, congestive heart failure)	Cardiac and vascular disorders are adverse events 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.
Choroidal detachment	Choroidal detachment is the separation of the choroid from the sclera of the eye as a result of leakage of fluid from the vessels of the choroid. It occurs when pressure inside the eyeball is very low, usually after trauma or intraocular surgery.
Eye infection or injury	Bacterial keratitis is an infection of the cornea (the clear, round dome covering the eye's iris and pupil) that causes pain, reduced vision, light sensitivity and tearing or discharge from the eye. It is an important cause of visual loss. The aetiology is diverse: bacterial, fungal, viral, protozoal or it may be polymicrobial in nature. Prescribed topical ocular medications can become contaminated and result in bacterial keratitis especially gram-

	negative infection with Pseudomonas, Serratia and Proteus species. Improperly handled of ocular solution can become contaminated by common bacteria. In addition eye traumatism by erroneous handling of the container may result in eye infection. Patient should follows specific instructions for use included in the PIL of the product
Medication error	Like other topically applied ophthalmic drugs, bimatoprost is absorbed into the systemic circulation. This may cause undesirable effects as seen with systemically absorbed ophthalmics. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Missing information	
Risk	**What is known**
Exposure in paediatric patients	The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.
Exposure inpregnancy and lactation	There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. [bimatoprost/timolol] should not be used during pregnancy unless clearly necessary. Animal studies with bimatoprost have shown reproductive toxicity. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice. Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. [Bimatoprost/timolol] should not be used by breast-feeding women.

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	23.09.2016	**Important identified risks** • Hyperpigmentation • Macular oedema • Choroidal detachment • Hypoglycaemia/diabetes • Cardiac and vascular disorders • Respiratory disorders • Corneal toxicity – dry eye • Co-administration with adrenaline • Hypersensitivity to any allergen • Masking hyperthyroidism signs **Important potential risks** • Increase in intraocular pressure • Off-label use (cosmetic use for stimulation of eyelash growth) **Missing information** • Use during pregnancy and lactation • Paediatric use	Initial version
1.0	04.11.2016	**NA**	Change of the description of the ATC code as per CZ comment during validation phase
1.0	29.05.2017	**Important identified risks** • Iris hyperpigmentation • Punctate keratitis • Cystoid macular oedema • Acute asthma and asthmatic symptoms • Bradycardia **Important potential risks** • Cardiovascular events (angina, hypotension, atrial fibrillation/arrhythmias, congestive heart failure) • Choroidal detachment	RMP update as per day70 RMS and day100 CMS Assessment report (alignment with summary of safety concerns of the originator) Update of SmPC/PIL as per recommendation of procedure PSUSA/00002961/201511. Alignement of RMP as per referral for multi-dose Novelia container (inclusion of eye infection or injury and medication

		• Drug interaction with calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics, digitalis glycosides, mydriatic agents, and CYP2D6 inhibitors **Missing information** • Exposure in paediatric patients • Exposure in pregnancy and lactation	error as potential risk)
1.0	07.09.2017	**Important identified risks** **Iris hyperpigmentation** **Punctuate keratitis** **Cystoid macular oedema** **Acute asthma and asthmatic symptoms** **Bradycardia** **Important potential risks** **Cardiovascular events (angina, hypotension, congestive heart failure)** Choroidal detachment Eye infection or injury Medication error **Missing information** Exposure in paediatric patients Exposure in pregnancy and lactation	RMP update as per day120 RMS Assessment report (alignment with summary of safety concerns of the originator) Alignment of RMP as per updated of SmPC/PIL at day 120 overall assessment report from RMS.
1.0	24.10.2017		Day 195 – SmPc/PIL update