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 (IOP). **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 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 World 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 development or slow the progression with medical and surgical means.

VI.2.2 Summary of treatment benefits

Bimatoprost is a highly potent and efficacious compound for lowering intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults both alone as well as together with beta-blockers.

Randomised controlled trials comparing different prostaglandis have found that bimatoprost and travoprost lowered intraocular pressure (IOP) effectively but bimatoprost showed a greater reduction in the mean IOP than did travoprost at 12 weeks and both are safe for ocular use. In addition, bimatoprost has an intraocular pressure IOP-lowering effect superior to that of latanoprost in glaucoma patients after switching from latanoprost.

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

Safety and efficacy of the product in children aged 0 to 18 years has not yet been established. Therefore, its use is not recombmended in these patients.
In addition, Bmatoprost has not been studied in patients with renal or moderate to severe hepatic impairment and should therefore be used with caution in 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	Some of these changes may be	These changes are solely

(the coloured part of the eye) *(Iris pigmentation)*	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. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish.	cosmetic in nature, and have not posed a health risk in any form. However, an ophthalmologist should be advised and patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation.
A disease characterized by blurred vision, dry eyes, a sensation of having a foreign body stuck in the eye, photophobia (sensitivity to bright light), burning sensations and watery eyes *(Punctate keratitis)*	Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy.	Monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.
Breathlessness or wheezing or increase of asthma symptoms *(Acute asthma and asthmatic symptoms)*	Bimatoprost has not been studied in patients with compromised respiratory function. While there is limited information available on patients with a history of asthma or COPD, there have been reports of exacerbation of asthma, dyspnoea and COPD, as well as reports of asthma, in post marketing experience. The frequency of these symptoms is not known.	Yes, by discontinuation of the treatment and immediate consultation of a doctor. Patients with COPD, asthma or compromised respiratory function due to other conditions should be treated with caution.
Allergy to benzalkonium	Bimatoprost contains the	Bimatoprost should be used

chloride, a substance contained in the solution *(BAC-related corneal toxicity)*	preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Eye irritation and discolouration of the soft contact lenses may also occur because of the presence of benzalkonium chloride. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy.	with caution in dry eye patients, in patients where the cornea may be compromised and in patients taking multiple BAK-containing eye drops. In addition, monitoring is required with prolonged use in such patients. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures, to avoid eye injury and contamination of the solution.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Increase in intraocular pressure	Patients using bimatoprost with other prostanglandin analogues should be monitored for changes to their intraocular pressure as there is a potential for the IOP-lowering effect of bimatoprost to be reduced.
Choroidal effusion	Choroidal effusion is an abnormal accumulation of fluid in the suprachoroidal space and is a common complication of glaucoma surgery. Choroidal effusion is a rare adverse effect which is not specific to bimatoprost but which has been also reported with the other prostaglandin analogue drops.
Cardiovascular events (bradycardia, angina & hypotension)	Cardiovascular events are related to systemic absorption of the drug. There have been a limited number of spontaneous reports of bradycardia or hypotension with bimatoprost eye drops, solution. These effects should be considered in elderly and in patients with cardiac, respiratory or neurological disease.
Off-label use (cosmetic use for stimulation of eyelash growth)	Hypertrichosis or increased lash length, pigmentation, or thickness is a relatively common side-effect of prostaglandin use. Patients must be advised that bimatoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension and should not be used for cosmetic purposes as its improper use is associated with both topical and systemic adverse events.
Reactivation of previous infective ocular disease	There have been rare spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with bimatoprost eye drops, solution. Bimatoprost should be used with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis. Bimatoprost has not been studied in patients with inflammatory

	ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

Missing information	
Risk	**What is known**
Use during pregnancy and lactation	There are no adequate data from the use of bimatoprost in pregnant women. Animal studies have shown reproductive toxicity at high doses. Bimatoprost should not be used during pregnancy unless clearly necessary. Bimatoprost did not impair fertility in rats up to doses of 0.6 mg/kg/day (at least 103-times the intended human exposure). It is unknown whether bimatoprost is excreted in human breast milk. Animal studies have shown excretion of bimatoprost in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue from bimatoprost therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Paediatric use	The safety and efficacy of bimatoprost in children aged 0 to 18 years has not yet been established, therefore its use in this population is not recommended.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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 (PL). 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

Not applicable

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

Version	Date	Safety concerns	Change
1.0	26.02.2015	**Important identified risks** • Macular oedema • Hyperpigmentation • Conjunctival hyperaemia • Hypertrichoses	Initial version

		• Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders • Adverse reaction to benzalkonium chloride **Important potential risks** • Corneal damage and hypersensitivity due to long term use of preserved eye drops • Ocular infections **Missing information** • Use in patients with renal or moderate to severe hepatic impairment • Potential interactions • Use during pregnancy and lactation	
2.0	28.09.2015	**Important identified risks** • Iris pigmentation • Punctate keratits • Acute asthma and asthmatic symptoms • BAC-related corneal toxicity **Important potential risks** • Increase in intraocular pressure • Reactivation of previous infective ocular disease • Choroidal effusion • Off-label use (cosmetic use for eyelash growth) **Missing information** • Use during pregnancy and lactation • Paediatric use	Day 70 + 100 assessors' comments