Bimatoprost

6.6.2014, Version 1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers)

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 worldwide, affecting 2% of individuals of European descent and up to 10% of individuals of sub-Saharan African descent over 50 years of age (11). Data from recent population-based surveys indicate that one in 40 adults older than 40 years has glaucoma with loss of visual function, which equates to 60 million people worldwide being affected and 8.4 million being bilaterally blind (21). As the population increases, so does the absolute number of glaucoma sufferers. In addition, with glaucoma prevalence increasing exponentially with age, glaucoma numbers are rising with the rapidly aging population. Accordingly, glaucoma patients are estimated to rise in number from 60 million in 2010 to nearly 80 million in 2020, with more than half in developed societies remaining undiagnosed (23).

VI.2.2 Summary of treatment benefits

Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers)

Over the last decade, prostaglandin (PG) F2α analogues (i.e. latanoprost and travoprost) and the structurally related prostamide bimatoprost have become widely used ocular hypotensive drugs, increasingly displacing β-blockers as first-line therapy. These preparations are regarded as the safest and most effective glaucoma drugs to date. According to reviews on the tolerability of PG analogues, once-daily treatment with bimatoprost 0.03% ophthalmic solution in patients with ocular hypertension or glaucoma is generally well tolerated, with a high rate of study completion in clinical trials (3, 4, 6, 20). The most commonly reported adverse events were conjunctival hyperaemia (mostly mild) and eyelash growth, occurring in 45% and 43% of bimatoprost recipients during the first year of treatment. The mechanism of action by which bimatoprost reduces intraocular pressure in humans is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow (2).

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of bimatoprost in children aged 0 to 18 years have not yet been established. Efficacy and safety have also not been studied in patients with renal or moderate to severe hepatic impairment, in patients with compromised respiratory function, in patients with heart block more severe than first degree or uncontrolled congestive heart failure, as well as in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-

closure glaucoma, congenital glaucoma or narrow-angle glaucoma. Also there are no adequate data from the use of bimatoprost in pregnant and lactating women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Darkening of the iris (Iris pigmentation)	Up to 10 % of patients develop iris darkening due to an increase in iris pigmentation. This can lead to differences in the appearance of the eyes, if only one eye is treated. A predisposing condition for this risk is a mixed iris colour. The change in eye colour is likely to be permanent.	Treatment with the lowest therapeutically effective dose and for the shortest recommended period, if possible.
Damage to the cornea caused by the preservative benzalkonium chloride (Punctate keratitis and benzalkonium chloride-related corneal toxicity)	Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause damage to the cornea. Bimatoprost 0.1 mg/ml eye drops contains 200 ppm benzalkonium chloride, Bimatoprost 0.3 mg/ml eye drops contains 50 ppm benzalkonium chloride.	The product should be used with caution in dry eye patients, in patients where the cornea may be compromised and in patients taking multiple benzalkonium chloride-containing eye drops. In addition, monitoring is required with prolonged use in such patients.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Recurrence of small hazy greyish areas surrounded by oedema located in the cornea (Reactivation of previous corneal infiltrates)	There have been rare spontaneous reports of reactivation of previous corneal infiltrates with bimatoprost 0.3 mg/ml eye drops, solution. Use the product with caution in patients with a prior history of significant viral eye infections (e.g. herpes simplex) or uveitis/iritis. There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.

Risk	What is known (including reason why it is considered a potential risk)
Recurrence of eye infection (Reactivation of ocular infections)	There have been rare spontaneous reports of reactivation of ocular infections with bimatoprost 0.3 mg/ml eye drops, solution. Use the product with caution in patients with a prior history of significant viral eye infections (e.g. herpes simplex) or uveitis/iritis. There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Build-up of fluid between the choroid (the blood vessel layer that nourishes the overlying retina) and the sclera, the white outer covering of the eye. (Choroidal effusion)	This risk has been reported in a case report of a 20-year-old woman using topical travoprost 0.004%/timolol 0.5% (fixed combination) (13). There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Increase in inner eye pressure (Increase in intraocular pressure)	There have been reports of paradoxical elevations in inner eye pressure following the use of two prostaglandin analogues at the same time. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended (26). There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Insufficient blood supply of the heart muscle (Angina)	The product can aggravate angina in patients with pre-existing disease. This risk is listed as adverse reaction in the SmPC of the prostaglandin F2α analogue latanoprost of Zentiva (26). There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Slowness of heartbeat (Bradycardia)	There have been a limited number of spontaneous reports of slow heartbeat with bimatoprost 0.3 mg/ml eye drops, solution. The product should be used with caution in patients predisposed to low heart rate. There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Low blood pressure (Hypotension)	There have been a limited number of reports of hypotension with bimatoprost 0.3 mg/ml eye drops, solution. The product should be used with caution in patients predisposed to low blood pressure. There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.

Risk	What is known (including reason why it is considered a potential risk)
Worsening of breathing (Compromised respiratory function)	Some cases of exacerbation of asthma, COPD and/or dyspnoea were reported in post marketing experience with the prostaglandin F2α analogue latanoprost of Zentiva (26) and travoprost of Alcon Laboratories (U.K) Limited (1). There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.
Use for not intended purpose (off-label use): cosmetic use for the stimulation of eyelash growth	It is possible to use this product off-label for the stimulation of eyelash growth. This would expose the user to all the possible adverse reactions of this product as well as reduce the normal intraocular pressure of the user. There is not enough evidence to clearly state that bimatoprost is responsible for the occurrence of this adverse reaction.

Missing information

Risk	What is known
Use in children and adolescents	The safety and efficacy of the product in children aged 0 to 18 years has not yet been established.
Use during pregnancy and lactation	There is not enough data from the use of bimatoprost in pregnant women. Animal studies have shown harm to the foetus at high maternotoxic doses. Bimatoprost should not be used during pregnancy unless clearly necessary. It is unknown whether bimatoprost passes into human breast milk. Animal studies have shown passing of bimatoprost into 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.

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

NA

VI.2.6 Planned post authorisation development plan

NA

Studies which are a condition of the marketing authorisation (if applicable)

The applicant has no imposed studies which are a condition of the marketing authorisation.

The reference product MAH performs an observational study and a paediatric investigation plan.

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

NA