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 world-wide, 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).

Based on comprehensive searches of peer-reviewed databases for published relevant evidence, several reviews examined risk factors for glaucoma. Strong and consistent evidence regarding the risk of developing glaucoma was found for elevated 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 (4, 11, 12, 21, 25). There is some evidence pointing to a lower IOP and risk of glaucoma in individuals performing activities consistent with overall good health such as regular, moderate exercise, a diet high in fruits and vegetables and a low intake of coffee and alcohol (19). The most common forms of glaucoma are age-related, beginning in midlife and progressing slowly but relentlessly. If detected early enough, disease progression can be slowed with drug and/or surgical treatment, underscoring the importance of identifying the disease in its earliest stages (11).

Glaucoma can be categorised by aetiology (primary, congenital or secondary) and by the appearance of the anterior chamber angle (i.e. the irido-corneal angle) as either open-angle glaucoma (OAG) or angle-closure glaucoma (ACG). The most common form of the disease, accounting for 75% of the incidence of glaucoma in Western developed countries, is OAG (6). OAG is distinguished from other optic neuropathies by slow progression over months to years. The disease is most often bilateral, but asymmetric. On average, there is 50% as much damage in the better eye as in the worse (21).

Primary OAG is most prevalent among individuals of African descent, who have almost 3 times the prevalence compared with individuals of Caucasian origin. In contrast, primary ACG is more prevalent in Asian populations, with Asians representing 87% of those with this form of glaucoma (23). Apart from being primary (i.e. of unknown

aetiology), both OAG and ACG can be secondary conditions. Secondary glaucoma refers to any case in which another disorder (e.g. injury, inflammation, vascular disease or diabetes mellitus) causes or significantly contributes to increased eye pressure, resulting in optic nerve damage and vision loss. Pseudo-exfoliation, characterised by accumulation of abnormal fibrillar extracellular material in intraocular tissues such as non-pigmented ciliary epithelium, iris pigment epithelium and trabecular endothelium, is the most common type of secondary OAG caused by an ophthalmologic condition (8).

Generally, glaucoma is seen in humans of advanced age. However, it can also occur in children. Childhood glaucoma is generally accompanied by raised IOP and decreased visual acuity. It is broadly grouped into congenital (primary developmental anomalies present in the drainage angle or secondary to other ocular or other developmental anomalies) and juvenile onset (8).

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)

According to the current scientific knowledge, glaucoma cannot be cured and damage caused by the disease cannot be reversed (8). 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 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 (3, 5, 8, 16, 21).

Today, medications available for reducing IOP in patients with ocular hypertension or glaucoma include topical β-adrenergic antagonists, prostaglandin analogues, carbonic anhydrase inhibitors, parasympathomimetics and α-adrenergic agonists. If monotherapy does not sufficiently decrease eye pressure, combinations of topical ophthalmic drugs may be used because the concomitant administration of agents with different modes of action has been shown to result in additive effects. Fixed combinations of commonly used drugs have also been developed (e.g., latanoprost plus timolol, bimatoprost plus timolol, travoprost plus timolol, dorzolamide plus timolol). While they may offer benefits of convenience, safety and cost, they limit individualisation of dosing (18).

Topical eye drops used to treat glaucoma lower the IOP by reducing the production rate of aqueous humour, by increasing the facility of aqueous outflow through the trabecular meshwork, by increasing the drainage of aqueous humour through the uveoscleral outflow pathway or by decreasing the pressure within the episcleral veins. Some ocular hypotensive drugs have effects on several of these parameters (7).

Pilocarpine is a direct acting parasympathomimetic that increases the outflow of aqueous humour; possible side effects include pain around or inside the eyes, brow ache, blurred or dim vision, myopia, allergic reactions, a stuffy nose, sweating, increased salivation, and occasional digestive problems. Today, pilocarpine is rarely used as first-line therapy, but considered as a third-line treatment option (17, 22).

Following their introduction in the 1970s, topically administered β-adrenergic receptor antagonists (e.g., timolol, betaxolol) have been the mainstay of therapy for more than 20 years. Today, timolol is still commonly used as adjunctive therapy. Non-selective β-blockers such as timolol inhibit both β-1 and β-2 adrenergic receptors; they are reasonably well tolerated locally. They are thought to lower IOP mainly by decreasing the β-adrenergic tone and inducing ciliary arteriolar vasoconstriction, thereby reducing aqueous humour production in the ciliary processes of the eye. However, due to systemic absorption after topical administration, they can cause adverse events by acting on β-1 adrenoceptors of the heart and on β-2 receptors in the bronchi. Therefore, topical β-blockers are contraindicated in patients with severe cardiovascular and pulmonary diseases. But even in otherwise healthy

glaucoma patients, these agents may negatively impact quality of life by causing respiratory difficulty, exercise intolerance, depression, fatigue or sexual dysfunction (17, 22).

Topical carbonic anhydrase (CA) inhibitors, i.e. dorzolamide and brinzolamide, lower IOP by decreasing the amount of aqueous humour. They may produce mild local adverse reactions but serious side effects occur very rarely. CA inhibitors are used as monotherapy and as adjunctive therapy to other antiglaucoma agents, mostly β-blockers (17, 22).

Alpha-2 adrenergic receptor agonists, such as brimonidine and apraclodine, reduce the production of aqueous humour; brimonidine has been shown to additionally enhance uveoscleral outflow. They are well tolerated; the most commonly reported adverse events with brimonidine therapy are ocular allergic reactions, but clinically significant effects on heart rate or blood pressure are generally not observed (17, 22).

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. Therefore they quickly replaced beta blockers as the preferred first-line agents for most patients with glaucoma (17, 22). 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).

Surgery is also an option for the treatment of glaucoma, especially when available medications are ineffective, contraindicated or when compliance is a problem. However, although glaucoma surgery may preserve current vision, it cannot restore vision already lost. Several possibilities exist: By using a high-energy laser beam, part of the trabecular meshwork can be shrunken, which causes other parts of the meshwork to stretch and open up. While laser surgery initially lowers IOP in almost all patients treated, the IOP starts to increase after some time in most of them. Trabeculectomy, i.e. removing a small piece of the trabecular mesh-work, is also performed. Sometimes a single surgical procedure may not lower eye pressure enough, in which topical treatment has to be continued or another trabeculectomy operation is required. Implantation of trabecular drainage is an option particularly for patients with secondary glaucoma or for children with congenital glaucoma. Possible complications from glaucoma surgery may include infection, bleeding, an IOP that remains too high or too low, and, in very rare cases, development of cataracts or visual field loss (8).

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 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.

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 and recurrence of eye infection (reactivation of previous corneal infiltrates or ocular infections)	There have been rare spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with bimatoprost 0.3 mg/ml eye drops, solution. Use the product with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis.
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)	Listed as important potential risk in the Risk Management Plan of the originator product Lumigan®. This risk has also been reported in a case report of a 20-year-old woman using topical travoprost 0.004%/timolol 0.5% (fixed combination) (13).
Increase in inner eye pressure (Increase in intraocular pressure)	There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended (26).
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).

Risk	What is known (including reason why it is considered a potential risk)
Slowness of heartbeat (bradycardia) and low blood pressure (hypotension)	There have been a limited number of spontaneous reports of bradycardia or hypotension with bimatoprost 0.3 mg/ml eye drops, solution. The product should be used with caution in patients predisposed to low heart rate or low blood pressure.
Worsening of asthma (asthma)	Some cases of exacerbation of asthma 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).
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.

Important missing information

Risk	What is known
Safety and efficacy in children and adolescents	The safety and efficacy of the product in children aged 0 to 18 years has not yet been established.
Safety in pregnant and lactating women	There are no adequate data from the use of bimatoprost in pregnant women. Animal studies have shown reproductive toxicity at high maternotoxic doses. Bimatoprost should not be used during pregnancy unless clearly necessary. 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.

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