VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The estimated number of people with vision loss from glaucoma range from 5.2 to 6.7 million. This is approximately 10% of the total number of affected persons, ranking glaucoma as the second most common cause of world blindness (6). Glaucoma can be categorised by cause (primary, congenital or secondary) and by the appearance of the anterior eye chamber angle (i.e. the angle between iris and cornea) as either open-angle glaucoma (OAG) or angle-closure glaucoma (ACG). The most common form of the disease, accounting for 75% of the occurrence of glaucoma in western developed countries, is OAG (2). OAG is distinguished from other eye nerve diseases by slow progression over months to years. The disease occurs most often in both eyes, but unequally. On average, there is 50% as much damage in the better eye as in the worse (7). Primary open-angle glaucoma (POAG) is a progressive disease of the eye nerve impairment of the visual field. The intraocular pressure (IOP) of the eye often exceeds its tolerance. POAG 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 (8). Apart from being primary (i.e. of unknown cause), both OAG and ACG can be caused by another disorder (e.g. injury, inflammation, blood vessel disease or diabetes mellitus) that causes or significantly contributes to increased eye pressure, resulting in eye nerve damage and vision loss. The most likely risk factors for developing glaucoma are elevated IOP, advancing age, non-Caucasian ethnicity and family history of glaucoma. There may also be an association between glaucoma and migraine, eye injury, myopia, long-term use of corticosteroids, high blood pressure, diabetes and smoking (1, 3, 5, 7, 9). The most common forms of glaucoma are age-related, beginning in midlife and progressing slowly but relentlessly.

VI.2.2 Summary of treatment benefits

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 (3). Lowering IOP remains the most readily modifiable risk factor to delay development of glaucoma in subjects with ocular hypertension (OH) and progression of POAG. A big study has shown that an additional 1 mmHg of IOP lowering reduces the risk of glaucoma progression by 10%. Participants of another study (AGIS-7 2000) who achieved the target IOP of <18 mmHg at each visit had very little deterioration of visual field over 96 months (6).

Patients with glaucoma and ocular hypertension frequently require multiple intraocular pressure (IOP)-lowering medications. Some patients are unable to either achieve or maintain their target IOP with monotherapy alone (4). In three controlled, double-masked clinical studies, brimonidine/timolol (twice daily) produced a clinically meaningful additive decrease in mean diurnal IOP compared with timolol (twice daily) and brimonidine (twice daily or three times a day) when administered as monotherapy (G2).

VI.2.3 Unknowns relating to treatment benefits

The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established and therefore, its use is not recommended in children or adolescents but not contraindicated. Brimonidine/timolol has not been studied in patients with closed-angle glaucoma. There are no

adequate data for the use of the brimonidine timolol fixed combination in pregnant women. It is not known if brimonidine is excreted in human milk. It is, however, excreted in the milk of the lactating rat.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in patients with sensitivity of the airways including current or previous asthma or the progressive pulmonary disease COPD (Use in patients with reactive airway disease including current or previous asthma or COPD)	Airway reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.	Brimonidine/timolol must not be used in patients with sensitivity of the airways including current or previous asthma or the progressive pulmonary disease COPD. Brimonidine/timolol should be used with caution in patients with mild/moderate progressive pulmonary disease COPD and only if the possible benefit is greater than the possible risk.
Heart diseases including heart rhythm disorders (where pacemakers do not help), heart failure, angina or low blood pressure (Cardiac diseases including conduction disorders (not controlled with a pacemaker), heart failure, angina or hypotension)	Decreased heart rate and depression have been reported during combined treatment with timolol and medicinal products called CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine). Congestive heart failure is an uncommon adverse reaction.	Patients with heart diseases called sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with a pacemaker, overt cardiac failure and cardiogenic shock must not take brimonidine/timolol. In patients with certain heart diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and low blood pressure therapy with beta-blockers should be critically assessed and the therapy with other medicinal products should be considered. Patients with heart diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to their negative effect on conduction time, betablockers should only be given with caution to patients with a heart disease called first degree heart block. As with oral beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid heart

Risk	What is known	Preventability
		rhythm disorders, heart attack or sudden death.
Use in newborns and children younger than 2 years **(**Use in neonates and infants (less than 2 years of age)**)**	In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants (less than 2 years of age) receiving brimonidine.	Brimonidine/timolol must not be used in children younger than 2 years.
Use in patients taking certain medication at the same time (monoamine oxidase (MAO) inhibitor, tricyclic antidepressants and mianserin) **(**Use in patients receiving monoamine oxidase (MAO) inhibitor therapy or antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)**)**	These medicinal products may interfere with brimonidine and precipitate severe high blood pressure.	Brimonidine/timolol must not be used in patients taking certain medication at the same time (monoamine oxidase (MAO) inhibitor, tricyclic antidepressants and mianserin). Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with brimonidine/timolol.
Drowsiness or sleepiness in children 2-7 years old **(**Somnolence in children 2-7 years of age**)**	In average 1-10 % of patients experience this adverse drug reaction. In children, the frequency and severity of the drowsiness or sleepiness are elevated.	Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤ 20 kg, should be treated with caution and closely monitored due to the high incidence and severity of drowsiness or sleepiness.
Late allergic reactions of the eye leading to increase in pressure inside of the eye (Ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) leading to increase in intraocular pressure)	Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solution 0.2 %, with some reported to be associated with an increase in IOP.	Patients with a history of any hypersensitivity should be closely monitored during treatment.
Deterioration of severe disturbances of blood flow in	Severe disturbance of blood flow may lead to dying off of fingers	Patients with severe disturbances of blood flow in the arms and legs (i.e. severe forms of Raynaud's

Risk	What is known	Preventability
the arms and legs (Deterioration of severe peripheral circulatory disturbances/disorders)	and toes.	disease or Raynaud's syndrome) should be treated with caution.
Blood pressure too low (Hypotension/bradycardia, also in surgical anaesthesia and in patients with severe renal impairment on dialysis)	Low blood pressure has been reported at an unknown frequency. The effect on the pressure inside of the eye or the known effects of oral beta-blockers may be stronger when timolol is given to the patients already receiving an oral beta blocker. Eye drops containing beta blockers may block the activity of adrenaline. There is a potential for low blood pressure and/or slow heartbeat when eye drops containing beta-blockers are taken concomitantly with medication such as oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine. Also, after the use of brimonidine, very rare (less than 1 in 10,000) cases of hypotension have been reported. Concomitant use of a beta-blocker with anaesthetic drugs may increase the risk for low blood pressure.	The response of these patients should be closely observed. The use of two eye drops containing beta blockers is not recommended. Before an operation the anaesthetist must be informed if the patient is receiving timolol. Caution is advised when using brimonidine/timolol with systemic antihypertensives.
Use of brimonidine/timolol in combination with medicine for the treatment of heart rhythm disorders (Drug interactions with antiarrhythmic agents)	Additive effects may lead to low blood pressure and low heartbeat when ophthalmic beta-blockers are taken in combination with medicine for the treatment of heart rhythm disorders (including amiodarone). Low blood pressure and low heartbeat are possible adverse drug reactions with unknown rate of occurrence.	Patients should tell their doctor that they are taking medicine for the treatment of heart rhythm disorders.

Risk	What is known	Preventability
Eye diseases such as thinning of the cornea, inflammation of the cornea, detachment of the vitreous humour from the retina and inflammation of the iris (Eye disorders (corneal erosion, superficial punctate keratitis, vitreous detachment, iritis, iridocyclitis))	1-10 % of patients experience thinning of the cornea, inflammation of the cornea and detachment of the vitreous humour from the retina. Inflammation of the iris is an adverse drug reaction to the treatment with brimonidine.	Eye drops containing beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Stopping of breathing (Respiratory arrest)	Brimonidine/timolol must not be used in patients with severe lung diseases. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some eye drops containing beta-blockers. Brimonidine/timolol should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. A causal relationship with brimonidine/timolol has not been established yet.
Low blood sugar may remain undiscovered because of mitigation of symptoms (Masking of acute hypoglycaemia)	Beta-blockers should be administered with caution in patients with risk factors for or a history of spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute low blood sugar level. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. A causal relationship with brimonidine/timolol has not been established yet.
An overactive thyroid may remain undiscovered because of mitigation of signs and symptoms (Masking of hyperthyroidism)	Beta-blockers may also mask the signs of an overactive thyroid. Brimonidine/timolol must be used with caution in patients with excess of acid in the body and untreated tumour of special cells (called chromaffin cells). A causal relationship with brimonidine/timolol has not been established yet.
A separation of two tissue layers in the eye called choroid and sclera (Choroidal detachment after filtration procedure)	A separation of two tissue layers in the eye called choroid and sclera has been reported with administration of eye drops containing timolol, acetazolamide or other active substances after a certain glaucoma surgery. A causal relationship with brimonidine/timolol has not been established yet.
Allergic reactions involving the whole body (Systemic allergic reactions)	This is an adverse drug reaction to the treatment with brimonidine.A causal relationship with brimonidine/timolol has not been established yet.
Memory loss (Amnesia)	Memory has been seen with ophthalmic beta-blockers. A causal relationship with brimonidine/timolol has not been established yet.
Disorders of blood vessels in the brain	Stroke and lack of blood supply to the brain have been seen with ophthalmic beta-blockers. A causal relationship with brimonidine/timolol has not been estab-

Risk	What is known (including reason why it is considered a potential risk)
(Cerebrovascular disorder)	lished yet.
Inflammation of the cornea (Keratitis)	Inflammation of the cornea has been seen with ophthalmic beta-blockers. A causal relationship with brimonidine/timolol has not been established yet.

Missing information

Risk	What is known
Use in patients with impairment of kidney or liver function (Use in patients with renal and hepatic impairment)	Brimonidine/timolol has not been studied in patients with impairment of kidney or liver function. Therefore, caution should be used in treating such patients.
Lack of experience in the use in children and adolescents (Data on the safety and effectiveness of brimonidine/timolol in children and adolescents)	The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established and therefore, its use is not recommended in children or adolescents.
Lack of experience in the use in patients with a different type of glaucoma called closed-angle glaucoma (Data on use in patients with closed-angle glaucoma)	Brimonidine/timolol has not been studied in patients with closed-angle glaucoma.
Lack of knowledge on the use in pregnant and breastfeeding women (Use in pregnancy and lactation)	There are not enough data for the use of the combination of brimonidine and timolol in pregnant women. Brimonidine/timolol should not be used during pregnancy unless clearly necessary. It is not known if brimonidine passes into human milk but it passes into the milk of the lactating rat.

VI.2.5 Summary of additional 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.

No additional risk minimisation measures are proposed for the products covered by this RMP.

VI.2.6 Planned post authorisation development plan (if applicable)

List of studies in post authorisation development plan

Not applicable, there are no planned post authorisation studies.

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

Not applicable

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

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	14.11.2013	Important identified: Use in neonates and infants (less than 2 years of age) Use in patients receiving monoamine oxidase (MAO) inhibitor therapy or antidepressants which affect nor-adrenergic transmission (e.g. tricyclic antidepressants and mianserin) Somnolence in children 2-7 years of age Increase in intraocular pressure Deterioration of cardiac disorders Deterioration of severe peripheral circulatory disturb-ances/disorders Hypotension/bradycardia, also in surgical anaesthesia and in patients with severe renal impairment on dial-ysis Eye disorders (corneal erosion, superficial punctate keratitis, vitreous detachment, iritis, iridocyclitis) Syncope Systemic allergic reactions Important potential risks Respiratory arrest Masking of acute hypoglycaemia Masking of hyperthyroidism (Deterioration of) anaphylactic reactions Choroidal detachment after filtration procedure Angioedema Memory loss Cerebrovascular disorder Keratitis	Initial version

Version	Date	Safety Concerns	Comment
		Missing information: Data on the safety and effectiveness of brimonidine/timolol in children and adolescents Data on use in patients with closed-angle glaucoma Data on interactions with the brimonidine/timolol fixed combination Sufficient data for the use of the brimonidine/timolol fixed combination in pregnant women Data on the excretion of brimonidine in human milk	
1.1	07.08.2014	Important identified: Use in patients with reactive airway disease including current or previous asthma or COPD Cardiac diseases including conduction disorders (not controlled with a pacemaker), heart failure, angina or hypotension Use in neonates and infants (less than 2 years of age) Use in patients receiving monoamine oxidase (MAO) inhibitor therapy or antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin) Somnolence in children 2-7 years of age Ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) leading to increase in intraocular pressure Deterioration of severe peripheral circulatory disturbances/disorders Hypotension/bradycardia, also in surgical anaesthesia and in patients with severe renal impairment on dialysis Drug interactions with antiarrhythmic agents Eye disorders (corneal erosion, superficial punctate keratitis, vitreous detachment, iritis, iridocyclitis) Important potential risks Respiratory arrest Masking of acute hypoglycaemia Masking of hyperthyroidism Choroidal detachment after filtration procedure Systemic allergic reactions Memory loss Cerebrovascular disorder Keratitis	Amendment according to assessment by reference member state Denmark

Version	Date	Safety Concerns	Comment
		Missing information: Use in patients with renal and hepatic impairment Data on the safety and effectiveness of brimonidine/timolol in children and adolescents Data on use in patients with closed-angle glaucoma Use in pregnancy and lactation	