Part VI: Summary of the risk management plan

Summary of risk management plan for <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*)

This is a summary of the RMP for <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*).

The RMP details important risks of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*), how these risks can be minimised, and how more information will be obtained about <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*)'s risks and uncertainties (missing information).

<Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*)'s SmPC and PL give essential information to healthcare professionals and patients on how <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*) should be used.

Important new concerns or changes to the current ones will be included in updates of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*)'s RMP.

I. The medicine and what it is used for

<Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*) is authorised for the reduction of IOP in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. It contains bimatoprost and timolol maleate as the active substances and it is given for ocular use.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*), together with measures to minimise such risks and the proposed studies for learning more about the products' risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal products can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine):

List of important risks and missing information	
Important identified risks	<u>Safety concerns related to the Bimatoprost:</u> • Iris hyperpigmentation • Punctate keratitis <u>Safety concerns related to the Timolol:</u> • Cystoid macular oedema • Bradycardia <u>Safety concerns related to the Bimatoprost and Timolol:</u> • Acute asthma and asthmatic symptoms
Important potential risks	<u>Safety concerns related to the Timolol:</u> • Choroidal detachment • Cardiovascular events (angina, hypotension, congestive heart failure)
Missing information	<u>Safety concerns related to the Bimatoprost and Timolol:</u> • Exposure in pregnancy and lactation • Exposure in paediatric patients

II.B Summary of important risks

Important identified risk relating Bimatoprost: Iris hyperpigmentation	
Evidence for linking the risk to the medicine	Iris hyperpigmentation has been identified as important identified risk because this effect is to be considered permanent. No evidence of harmful consequences of this adverse effect has been found, and the only disadvantage

	appears to be potential heterochromia between the eyes in unilaterally treated patients: the heterochromia is likely to be permanent, or very slowly reversible.
Risk factors and risk groups	The effect is especially seen in patients with green-brown, blue/gray-brown or yellow-brown irides. Eyes with mixed-colour irides containing brown areas are especially susceptible to colour change. However, it is likely that this observation is due to changes in iris color, which can be easier observed in these patients, rather than in patients with brown irides. Increased iris pigmentation usually appears in the first months of the prostaglandin analogues medication and develops in nearly all those eyes that developed iris darkening within the first 5 years of treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.4 and 4.8 PIL sections: 2 and 4 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Important identified risk relating Bimatoprost: Punctate keratitis	
Evidence for linking the risk to the medicine	Punctate keratitis has been identified as important identified risk because the frequency of this adverse event was found to be common. No evidence of harmful consequences of this adverse effect has been found. Most patients recover fully.
Risk factors and risk groups	The risk of developing punctate keratitis is increased in patients who: • have had a cataract surgery in the past, • have dry eyes, have or have had any problem with the cornea • wear contact lenses, • have had a viral infection or inflammation of the eye.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 PIL sections: 2 and 4 Legal status of the product: prescription only medicine.

	Additional risk minimisation measures: No risk minimisation measures

Important identified risk relating Timolol: Cystoid macular oedema	
Evidence for linking the risk to the medicine	Cystoid macular oedema has been identified as important identified risk because it is potentially serious adverse event.
Risk factors and risk groups	Known risk factors for macular oedema are the following: • intraocular surgery • retinal vein occlusions • ocular inflammatory disease • diabetic retinopathy.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.4 and 4.8 PIL sections: 2 and 4 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Important identified risk relating Timolol: Bradycardia	
Evidence for linking the risk to the medicine	Bradycardia has been identified as important identified risk because it is potentially serious adverse events.
Risk factors and risk groups	The risk of developing bradycardia is increased in patients with a medical history of bradycardia. A number of patients reported previous fainting episodes or chronic low blood pressure. Moreover, there is an increased risk of bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.3, 4.5, 4.8 and 4.9 PIL sections: 2 and 4

	Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Important identified risk relating Bimatoprost and Timolol: Acute asthma and asthmatic symptoms	
Evidence for linking the risk to the medicine	Asthma has been identified as important identified risk because there have been reports of asthma and asthma exacerbation during treatment with bimatoprost/timolol.
Risk factors and risk groups	The risk of developing asthma and asthma exacerbation is increased in patients who have or have had respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/or long-standing cough).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.3, 4.4, and 4.8 PIL sections: 2 and 4 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Important potential risk relating Timolol: Choroidal detachment	
Evidence for linking the risk to the medicine	Choroidal detachment has been identified as important potential risk because it is potentially serious adverse event.
Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.4 and 4.8 PIL sections: 2 and 4 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Important potential risk relating Timolol: Cardiovascular events (angina, hypotension, congestive heart failure)	
Evidence for linking the risk to the medicine	Cardiovascular events have been identified as important potential risk because these are potentially serious adverse events.
Risk factors and risk groups	The risk of developing cardiovascular events is increased in patients with: • coronary heart disease, • angina, • cardiac failure, • severe peripheral circulatory disturbance/disorders • those on therapy with beta-blockers.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9. PIL sections: 2 and 4 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Missing information relating to Bimatoprost and Timolol: Exposure in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PIL section 2 Legal status of the product: prescription only medicine. Additional risk minimisation measures: No risk minimisation measures

Missing information relating Bimatoprost and Timolol: Exposure in paediatric patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 5.1 PIL section 2 Legal status of the product: prescription only medicine.

	Additional risk minimisation measures: No risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*).

II. C.2 Other studies in post-authorisation development plan

There are no studies required for <Invented name> 0.3mg/ml + 5mg/ml eye drops, solution (*bimatoprost* and *timolol maleate*).