VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Glaucoma is a group of eye conditions resulting in optic nerve damage, which may cause loss of vision. High pressure inside the eye (intraocular pressure) usually, but not always, causes this damage.

Glaucoma is one of the leading causes of blindness in the world. Glaucoma can damage vision gradually and the patient may not notice any loss of vision until the disease is at an advanced stage. The most common type of glaucoma, primary open-angle glaucoma, has no noticeable signs or symptoms except gradual vision loss.

Early diagnosis and treatment can minimize or prevent optic nerve damage and limit glaucoma-related vision loss. It's important to get eyes examined regularly.

It is estimated 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. Even in developed countries, half of glaucoma cases are undiagnosed.

Pseudoexfoloative glaucoma is an OAG and has been widely described as the result of the accumulation of pseudoexfoliative material, which obstructs the trabecular meshwork leading to an increase in IOP levels. Pseudoexfoloative glaucoma increases with age and has a higher prevalence in patients between 60 and 70 years of age. Men are more affected than women, but this gender association is not always reproducible. Although the prevalence in the general population varies from country to country, different studies describe a higher prevalence of Pseudoexfoloative glaucoma in Scandinavia (3).

Several risk factors can be associated with the development of glaucoma including:

- Increased intraocular pressure
- Age (over age 60)
- Ethnic background
- Genetics (family history)
- Medical conditions (e.g. diabetes, heart diseases, high blood pressure and hypothyroidism)
- Other eye conditions (severe eye injuries, eye tumors, retinal detachment, eye inflammation, lens dislocation, certain types of eye surgery)
- Long-term corticosteroid use

Glaucoma is not considered to affect mortality in patients.

VI.2.2 Summary of treatment benefits

For the treatment of glaucoma, several options as an initial intervention are available, namely surgical, laser or medical. Medical management is the general standard of practice for the initial treatment of open-angle glaucoma.

Treatment with dorzolamide / timolol has a greater IOP lowering effect than that of monotherapy. It is also thought that the combination therapy of dorzolamide / timolol has considerable clinical value in that the combination offers fewer daily drops than concomitant therapy which, through improved convenience, may increase patient compliance; the potential risk of confusion between the two bottles

is overcome, which may also improve patient compliance; and the risk of elimination of the first drop from the cul de sac by the instillation of the second drop is completely avoided, since both agents are instilled uniformly in a pre-mixed solution.

VI.2.3 Unknowns relating to treatment benefits

Significant safety and efficacy differences among different races were not detected in any of the clinical trials.

Dorzolamide / timolol is not recommended for use in paediatric patients due to a lack of data on safety and efficacy. Dorzolamide / timolol can be and has been used for the treatment of increased IOP or glaucoma in children (congenital glaucoma). However, the first line treatment of congenital glaucoma is surgery. In some cases when surgery can't be performed immediately, eye drops might be prescribed for periodical use.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Respiratory problem such as bronchial asthma / a history of bronchial asthma or severe chronic obstructive bronchitis	Bronchospasm occurred predominantly in patients with pre-existing bronchospastic disease. Serious respiratory ADRs are possible and in rare cases life-threatening. Concomitant beta-blockers or other antiadrenergic drugs could potentiate the effects of timolol. The overall risk is expected be lower with topical beta-blockers compared with systemic beta-blockers.	Beta-blockers should not be used in these conditions.
Coronary heart disease, disturbances of heart rate, heart failure	Beta-blockers can worsen these conditions. Serious cardiac ADRs are possible and in rare cases life-threatening. Pre-existing disease, other beta-blockers or antiadrenergic drugs increases the risk. The overall risk is expected be lower with topical beta-blockers compared with systemic beta-blockers.	Beta-blockers should not be used in these conditions.
Poor blood circulation disease	Beta-blockers can worsen the symptoms of some circulatory disorders like claudication, Raynaud's phenomenon or cold hands and feet. However, most adverse events are mild and self-limited. Pre-existing disease, concomitant use of other beta-blockers or antiadrenergic drugs may increase the risk. The overall risk is expected be lower with topical beta-blockers compared with systemic beta-blockers. The risk is labelled (in product information), and the potential impact is expected to be low.	
Severe hypersensitivity reactions	Known hypersensitivity to any ingredient or excipient.	

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Masking of symptoms of low blood sugar in patients with diabetes mellitus	Beta-blockers should be administered with caution in patients subject to low blood sugar or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of low blood sugar. The risk is labelled (in product information), and the potential impact is expected to be low.
Concomitant Use with Other Oral or Topical Carbonic Anhydrase Inhibitors or Beta-blockers	The effect on intra-ocular pressure or the known effects of other oral or topical carbonic anhydrase inhibitors or beta-blockers may be potentiated when cosopt is given to the patients already receiving a systemic carbonic anhydrase inhibitors or beta-blockers.
Choroidal Detachment	Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures. The mechanism is speculated to supersensitivity to previously received topical IOP-lowering drugs after filtration surgery, resulting in hypotony.
Corneal edema	Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema

Important missing information

Risk	What is known
Limited information on use of the dorzolamide-timolol combination or either drug alone in patients with kidney or liver impairment	It is unlikely that kidney or liver impairment will lead to problems. However, patient with severe kidney failure should be treated with extreme caution.
Use in pregnancy or in breast-feeding women	In animal studies tafluprost has been shown to cause Embryotoxicity. Timolol is excreted in breast milk. Therefore, the tafluprost-timolol combination should not be used in pregnant or breast-feeding women.
Use in children younger than 2 years of age	Children younger than 2 years of age have not been studied in clinical trials. Therefore, the dorzolamide-timolol combination is not recommended for use in children younger than 2 years of age.

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

All medicines have a 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.

The SmPC and the PL for COSOPT can be found in the Competent Authority web-page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Santen is not planning to perform post authorisation studies at the moment.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan

Version	Date	Safety Concerns	Comment
1.0	At time of Marketing Authorization application for Cosopt PFMD on 20/03/2017	Identified Risks ● Reactive airway disease, bronchial asthma, or severe COPD ● Sinus bradycardia, sino-atrial block, second- or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock ● Hypersensitivity Potential Risks ● Vascular disorders ● Masking of hypoglycemic symptoms in patients with diabetes mellitus ● Masking of thyrotoxicosis ● Surgical anesthesia	

Version	Date	Safety Concerns	Comment
		● Concomitant use with other oral or topical carbonic anhydrase inhibitors or beta-blockers ● Choroidal detachment ● Corneal edema in patients with low endothelial cell counts ● Anaphylaxis Missing information ● Use in renal impairment ● Use in hepatic impairment ● Use in pregnancy ● Use in lactation ● Use in children younger than 2 years of age	
2.0	27/11/2017	Identified Risks ● Systemic beta-blockade associated side effects including worsening of pre-existing cardiac and vascular disorders ● Respiratory disorders (including bronchospasm, worsening of pre-existing reactive respiratory diseases) ● Severe hypersensitivity reactions Potential Risks ● Choroidal detachment ● Corneal edema in patients with low endothelial cell counts ● Masking of hypoglycemic symptoms in patients with diabetes mellitus ● Drug interaction with other oral or topical beta-blocking agents or carbonic anhydrase inhibitors, and CYP2D6 inhibitors ● Urolithiasis Missing information ● Use in pregnancy or in breast-feeding women ● Use in patients with hepatic impairment or severe renal impairment ● Use in children younger than 2 years of age	Identified risks, potential risks and missing information were updated based on the discussion with authority at the time of Marketing Authorization application
2.1	12/04/2018	'In patients with low endothelial cell counts' removed from corneal edema	Based on the discussion with authority at the time of Marketing Authorization application