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. Abnormally 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.

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.

Several different medicinal products can be used in the treatment of glaucoma. However, the introduction of prostaglandin analogues (PGAs) like tafluprost significantly changed the treatment practice of glaucoma. The benefit of IOP reduction in the treatment of glaucoma has been confirmed in large clinical trials, and PGAs are considered the first line treatment for IOP. Although prostaglandins are highly effective IOP-reducing agents in a number of patients, combined treatment with two or many drugs is sometimes needed for adequate control of increased intraocular pressure. Other useful medications are β-adrenergic antagonists (e.g. timolol, betaxolol), cholinergic agonists (e.g. pilocarpine), α-adrenergic agonists (e.g. brimonidine) or carbonic anhydrase inhibitors (e.g. dorzolamide, brinzolamide)

The most frequently used combination of prostaglandins is with the beta-blocking agent timolol. There are several prostaglandin-timolol combination products on the market. The advantage of combination products is that the treatment regimen becomes simpler for the patient thereby improving the compliance with better intraocular pressure control.

The tafluprost-timolol combination is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Two pivotal phase III trials have been performed in Europe. Altogether 484 patients have received the tafluprost-timolol combination in these studies. The tafluprost-timolol combination was compared to tafluprost and timolol therapies when they were given as monotherapy and to tafluprost and timolol when they were given concomitantly.

The tafluprost-timolol combination is a very effective intraocular pressure reducing medicine. The combination was more effective than tafluprost or timolol given as monotherapy, and at least as effective as tafluprost and timolol given concomitantly. The tafluprost-timolol combination was particularly useful in patients with high intraocular pressure in whom pressure reductions > 10 mmHg were commonly seen.

VI.2.3 Unknowns relating to treatment benefits

In the main studies practically all patients were white Caucasians aged between 18 and > 80 with most patients aged over 60. Supporting studies in Asians have been performed in Japan showing efficacy of the tafluprost-timolol combination in this population. There is no evidence to suggest that results would be any different in other patient populations with open-angle glaucoma or increased intraocular pressure.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hyperpigmentation (darkening of the colour of the skin around the eyes or change the colour of your iris)	Hyperpigmentation in the iris and eyelids is commonly observed with tafluprost as with other drugs in this class. No precancerous events related to hyperpigmentation has been claimed to be associated with tafluprost treatment.	Some patients are more susceptible for hyperpigmentation than others. The risk is very difficult to minimise in these patients.
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.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
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.
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.
Masking of symptoms of overactivity of the thyroid gland	Beta-blockers may also mask the signs of overactivity of the thyroid gland. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms. The risk is labelled (in product information), and the potential impact is expected to be low.
Surgical Anesthesia	Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol. Previous adverse events with surgical anesthesia, respiratory or cardiac comorbidities, other concomitant 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.
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.
Anaphylactic reaction	Systemic and topical β-blockers may antagonize the effects of epinephrine at the β-adrenergic receptor. In patients receiving β-blockers, anaphylaxis may be severe, prolonged, or resistant to the usual doses used to treat anaphylactic reactions.

Important missing information

Risk	What is known
Limited information on use of the tafluprost-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 pregnant or 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 and adolescents	Children and adolescents have not been studied in clinical trials. Therefore, the tafluprost-timolol combination is not recommended for use in children or adolescents below age 18.

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.

The Summary of Product Characteristics and the Package leaflet for Taptiqom 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

The current version of the Risk Management Plan is the first one for the tafluprost-timolol combination.