## 7.2 Part VI.2 Elements for a Public Summary

### 7.2.1 Part VI.2.1 Overview of disease epidemiology

Glaucoma has been established as the second leading cause of world blindness, which may affect 60.5 million people worldwide in 2010, and 79.6 million in 2020, and approximately 74% of glaucoma patients have primary open-angle glaucoma (POAG) (Cheng et.al 2012).

### 7.2.2 Part VI.2.2 Summary of treatment benefits

#### 7.2.2.1 Current (gold) standards of treatment

The treatment of glaucoma focuses mainly on lowering intraocular pressure (IOP). The target IOP is often set to a level 20% to 30% of IOP reduction, and consequent large IOP reduction beyond 30% or even 40% in cases of advanced glaucoma.

In the last two decades, several novel classes of topical IOP-lowering drugs have been available, and now there are more choices in the treatment of glaucoma. A recent meta-analysis of the IOP-lowering effect of glaucoma drugs showed a maximum mean IOP reduction of 33% from baseline IOP in the case of monotherapy. However, many patients require more than one medication to achieve adequate IOP reduction.

More recently, to maximize patient medication adherence and quality of life, several fixed combinations of commonly used IOP-lowering medications have been developed. Current commercially available, fixed combination drugs mostly include the topical beta-blocker 0.5% timolol combined with a prostaglandin analogue (PGA), an alpha-adrenoceptor agonist (AA) or a topical carbonic anhydrase inhibitor (CAI). More and more clinical trials are published to evaluate the efficacy of these fixed-combination options (Cheng et.al 2012).

#### 7.2.2.2 Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.)

Dorzolamide + Timolol is a combination of dorzolamide hydrochloride, an ophthalmic carbonic anhydrase inhibiting active substance and timolol maleate, an ophthalmic beta-blocking active substance, both of which lower raised pressure in the eye in different ways.

Dorzolamide + Timolol is prescribed to lower raised pressure within the eye in the treatment of glaucoma when beta-blocker eye drops used alone are not adequate.

#### 7.2.2.3 Post-authorization data which impacts on efficacy

This is a generic product. The efficacy profile is based on the originator/ reference product. No post-authorization data is available which is known to impact the efficacy of the product.

### 7.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Safety of Dorzolamide + Timolol has been demonstrated in a study with pediatric patients under six and greater than or equal to two years of age. The efficacy in these patients was not established. Efficacy and safety of Dorzolamide + Timolol in children under 2 years of age have not been established. The safe use of the medicinal product during pregnancy has not been established.

### 7.2.4 Part VI.2.4 Summary of safety concerns

**Table 7-5 Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Cardiac disorders | In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered.<br><br>Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. | Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block. |
| Respiratory disorders | Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration | Dorzolamide/Timolol should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease |

| Risk | What is known | Preventability |
|---|---|---|
| | of some ophthalmic beta-blockers. | (COPD) and only if the potential benefit outweighs the potential risk. |
| Hypoglycaemia | Beta-blockers may mask the signs and symptoms of acute hypoglycaemia and may also mask the signs of hyperthyroidism. | Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia. |
| Choroidal detachment | Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures. | If such reactions occur, discontinuation of Dorzolamide/Timolol should be considered. |
| Hypersensitivity reactions (including anaphylactic and serious skin reactions) | As with other topically-applied ophthalmic agents, this medicinal product may be absorbed systemically. The active substance dorzolamide is a sulphonamide. Therefore the same types of adverse reactions found with systemic administration of sulphonamides may occur with ocular useLocal ocular adverse reactions similar to those observed with dorzolamide hydrochloride eye drops, have been seen with the fixed combination of dorzolamide and timolol.<br><br>While taking β-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. | If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation. |
| Dryness of eyes | Ophthalmic β-blockers may induce dryness of eyes. | Patients with corneal diseases should be treated with caution. |
| Drug interaction with β-agonists (e.g. adrenaline) | β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. | The anaesthesiologist should be informed when the patient is receiving timolol. |

| Risk | What is known | Preventability |
|---|---|---|
| Potentiated systemic beta-blockade during combined treatment with CYP2D6 inhibitors and timolol | Ocular administration of timolol delivers the drug directly to the systemic circulation [4]. The main path of timolol metabilsation is via the hepatic enzyme CYP2D6 [5].<br>Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol. | Treatment of a CYP2D6 inhibitor together with dorzolamide/timolol eye drops should be performed carefully. |

**Table 7-6 Important potential risks**

| Risk | What is known<br>(Including reason why it is considered a potential risk) |
|---|---|
| Vascular disorders | Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. |

### 7.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

None

### 7.2.6 Part VI.2.6 Planned post authorization development plan

None

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

**Table 7-7 Major Changes to the Risk Management Plan over time**

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 01 | 26 Oct 2012 | <u>Identified risks:</u><br>Cardiac disorders<br>Respiratory disorders<br>Hypoglycaemia<br>Choroidal detachment<br>Hypersensitivity reactions (including anaphylactic and serious skin reactions)<br><br><u>Potential risks:</u><br>Vascular disorders | Version 01 prepared to comply with the new regulatory requirement of a RMP for every application leading to a Marketing Authorization irrespective of the procedure. |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | Missing information:<br>None | |
| 02 | 23 Apr 2013 | Identified risk: Potentiated systemic beta-blockade during combined treatment with CYP2D6 inhibitors and timolol | Risk added in answer to the Assessment Report RMP version 2.0 of the Final Variation Assessment Report DK/H/1435/001/II/012, dated 24 Apr 2013. |