13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Glaucoma is a group of eye diseases which result in damage to the optic nerve (nerve which carry signals to and from eye and brain) and vision (eyesight) loss. It 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 a certain type called primary OAG (POAG) (a disorder of optic nerve (nerve which carries signals to and fro brain and eye) that is long term, continuous, and irreversible, usually caused by increased fluid pressure inside eye) [Cheng JW, 2012].

Glaucoma is a progressive optic neuropathy (gradual damage to the optic nerve) that leads to blindness if left untreated. Risk factors include increased IOP (fluid pressure inside the eye), advanced age, African ancestry and positive family history. Several types of glaucomas have been described: acute (sudden) and chronic (long term), secondary (glaucoma that occurs as a consequence of another eye problem) and primary. POAG (chronic) is the most common [Coleman AL, 2001].

The occurrence of OAG and IOP increases with age [Hitzl W, 2006]. Ageing is associated with a 1.5% increase per year. Prevalence of OAG and increased IOP are race-related. For example, in Japan there is a lower average normal IOP than in Europe and similar OAG occurrence rate to Europe at a lower mean IOP [Johnson GJ, 2003]. The occurrence rates of OAG in white Europeans, Americans and Australians are similar when the figures are age-adjusted. Black populations in the Caribbean and the USA have higher occurrence of OAG than those of European origin. West African patients seen in facilities in Europe and North America present with symptoms of OAG at an earlier age than Europeans, and OAG appears to progress more rapidly.

13.2.2 Part VI.2.2 Summary of treatment benefits

The treatment of glaucoma focuses mainly on lowering 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 (externally applied) 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 average IOP reduction of 33% from baseline IOP in the case of monotherapy (single drug therapy). 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 or a topical CAI. More and more clinical trials are published to evaluate the efficacy of these fixed-combination options [Cheng JW, 2012].

Brinzolamide is a thienothiazine sulfonamide and is an inhibitor of CA-II. Inhibition of CA in the ciliary processes of the eye decreases aqueous humor secretion by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in IOP.
Brinzolamide is indicated to decrease elevated IOP in:
- OH
- OAG
as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers and prostaglandin analogues.

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.

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of brinzolamide in patients below the age of 18 have not been established and its use is not recommended in these patients. However, there is limited experience in children. The safety and efficacy of brinzolamide have been studied in a small number of pediatric patients less than 6 years of age. There are no or limited amount of data from the use of brinzolamide e in pregnant women. Studies in animals have shown reproductive toxicity. Brinzolamide is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether brinzolamide /metabolites are excreted in human milk. Animal studies have shown the excretion of brinzolamide in breast milk. Brinzolamide should only be used during breast-feeding when the benefit of breast-feeding for the child and the benefit of therapy for the woman outweigh the possible risks.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
Cornea (the transparent layer forming the front of the eye) swelling resulting from failure of the corneal endothelium (layer on the inner surface of the cornea) to maintain state of dehydration (fluid loss) [Corneal Decompensation]	Corneal epithelium defect, and corneal epithelium disorder (defects and disorders of superficial layer of the cornea) were uncommon side effects in patients taking brinzolamide. Corneal swelling is a rare side effect and corneal disorder is a side effect with unknown frequency in patients taking brinzolamide.	Before taking brinzolamide, the doctor or pharmacist should be advised if the patient have any cornea problems. The possible effect of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas particularly in patients with low number of cells in endothelial layer of cornea and also in patients with diabetes mellitus (high sugar levels in blood), or corneal dystrophies (a group of genetic eye disorders in which abnormal material often accumulates in the clear outer layer of the eye).

Risk	What is known	Preventability
		Careful monitoring of these patients when using brinzolamide is recommended in the labeling.
A condition that occurs when the body produces excessive quantities of acid or when the kidneys are not removing enough acid from the body [Metabolic acidosis]	Acid-base disturbances have been reported with oral CAIs (drug that reduces pressure within the eye). Electrolyte imbalance (imbalance of certain ionized salts such as bicarbonate, calcium, chloride, magnesium, phosphate, potassium, and sodium in the blood.) and development of an acidotic state has been observed with brinzolamide overdose.	Patient should not take brinzolamide if suffers from too much acidity in the blood (a condition called hyperchloremic acidosis) Doctor should carefully monitor the patient's blood electrolyte levels and blood pH levels. Acid-base disturbances have been reported with oral CAIs and those patients with significant abnormalities of essential structures of kidney should only receive brinzolamide after careful consideration of the risk benefit balance due to the possible risk of metabolic acidosis. Also, it states that brinzolamide has not been studied in patient with severe renal (kidney) impairment (creatinine clearance < 30 ml/min) or in patients with hyperchloremic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, brinzolamide is contraindicated in such patients.

Table 13-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Drug induced side effects affecting the heart and its blood vessels [Cardiovascular events]	Decreased or reduced heart function, palpitations (a sensation in which a person is aware of an irregular, hard, or rapid heartbeat), decreased heart rate, difficulty breathing and shortness of breath were uncommon side effects in patients taking brinzolamide. Chest pain and irregular heart rate were rare side effects in patients taking brinzolamide. Decreased blood pressure, increased blood pressure,

Risk	What is known (Including reason why it is considered a potential risk)
	increased heart rate, and swelling of the extremities are side effects with unknown frequency in patients taking brinzolamide.
Long term use of preserved eye drops	No long term data are available on the use of brinzolamide as adjunctive (an additional) therapy to travoprost. Since brinzolamide contains benzalkonium chloride, close monitoring is required while prolonged use in dry eye patients, or in conditions where the cornea is compromised.

Table 13-7 Missing information

None requiring evaluation beyond routine pharmacovigilance and routine risk minimization activities.

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

None

13.2.6 Part VI.2.6 Planned post authorization development plan

None

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

Table 13-8 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	31 Jan 2017	Important identified risks • Corneal Decompensation • Metabolic Acidosis Important potential risks • Cardiovascular events • Long term use of preserved eye drops Missing information • None requiring evaluation beyond routine pharmacovigilance and routine risk minimization activities	Based on CMS HU Day 50 Assessment report Part II: Module SVIII “Summary of the safety concerns” was updated. Accordingly Part V.1, V.3, VI.1.1, VI.1.4 and VI.2.4 were also updated. Annex 2 and Annex 3 were also updated.
2.1	2 May 2017	N/A	Based on the comments made by RMS NL and CMS RO during clock stop the word “important” was deleted from the phrase “important missing information” in the summary of safety concerns in Part II: Module

Version	Date	Safety Concerns	Comment
			SVIII and Part VI