2.2 Introduction

A) Drug Substance Travoprost

International Nonproprietary Name (rINN): Travoprost

Structural formula:

Molecular formula:
Molecular weight:

Chemical name:
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Travoprost, a prostaglandin $F_{2\alpha}$ analogue, is a highly selective full agonist which has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of the intraocular pressure in man starts about 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Data on adjunctive administration of Travoprost with Timolol 0.5% and limited data with brimonidine 0.2% were collected during clinical trials that showed an additive effect of Travoprost with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. Studies in rabbits have shown peak concentrations of 20 ng/g of the free acid in aqueous humour one to two hours after topical dosing of Travoprost. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Following topical ocular administration of Travoprost to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25 pg/ml or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit before 1 hour post-administration. Due to the low plasma

concentrations and rapid elimination following topical dosing, the elimination half-life of active free acid in man could not be determined.

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin $F_{2\alpha}$ which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain.

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is necessary in these patients.

B) Drug Substance Timolol maleate

International Nonproprietary Name (rINN): Timolol Maleate
Structural formula:

Molecular formula:
Molecular weight:

Chemical name:

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist which will restore the usual biological response.
Unlike miotics, Timolol reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular opacities when the pupil is constricted is avoided. When changing patients from miotics to Timolol, refraction might be necessary when the effects of the miotic have passed.
Diminished response after prolonged therapy with Timolol has been reported in some patients.

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

Glaucoma is a group of eye disorders traditionally characterized by progressive damage to the eye, at least partly due to elevated intraocular pressure (IOP). It is the leading cause of irreversible blindness in the world and the second leading cause of vision loss after cataract, which is reversible surgically. Primary open-angle glaucoma (POAG) is the most common form of glaucoma, accounting for about 60 to 70% of all glaucomas. Both eyes are generally affected, but not necessarily equally. Risk factors for POAG are elevated intraocular pressure, advanced age, black race, and family history. Eyes with POAG develop progressive peripheral visual field loss followed by central field loss, in a characteristic pattern, usually but not always in the presence of elevated IOP.

Travoprost 40 μg/ml/Timolol 5 mg/ml Eye Drops, Solution is indicated for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
The active components of Travoprost/Timolol Eye Drops, Travoprost and Timolol maleate have each been approved as first line therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension in the EU.

The potential interaction of the active ingredients Travoprost and Timolol was discussed. Considering that Travoprost and Timolol are two distinct pharmacological agents, which act by different mechanisms of action and the lack of interaction reports in the literature, support the view that the two agents do not impact significantly on the pharmacodynamics of one another. Low plasma levels and rapid removal of the free acid of Travoprost argues against a significant pharmacological interaction occurring between these two mechanistically distinct agents. Furthermore, no signs of ocular or systemic toxicity were observed in toxicology studies conducted in rabbits and monkeys after chronic administration. In conclusion, these data suggest that the individual agents dosed at the clinical concentrations and intended regimen do not interact pharmacologically.

No studies evaluating drug-drug interactions have been performed. Since Travoprost undergoes a biotransformation pathway similar to endogenous prostaglandin-F2α, and since systemic levels of active metabolite following topical ocular administration are negligible, interactions with concomitant medications in patients receiving topical ocular doses is considered to be unlikely. *In vitro* experiments have shown Travoprost free acid to be moderately bound (about 80%) to plasma proteins in humans, indicating drug-drug interactions through protein binding to be unlikely.

From the results of this study, it is also concluded that administration of Travoprost/Timolol eye drops did not result in a change in the systemic exposure to either Timolol, as compared to Timolol 5 mg/ml alone, or Travoprost, as compared to Travoprost given in monotherapy. Therefore, the lack of drug-drug interaction between Timolol and Travoprost was concluded.