2.2 Introduction

Drug Substance Bimatoprost

Name (INN) : Bimatoprost

Structural formula :

Molecular formula :

Molecular weight :

Chemical name :

Mechanism of Action:

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$. It is currently indicated for the reduction of elevated IOP in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers. Bimatoprost is a highly efficacious and long-acting ocular hypotensive agent. It is pharmacologically unique and does not exert its effects by stimulating any known major receptor subtype. It represents a new generation of IOP-lowering drugs that exerts a profound effect on IOP by a mechanism that exclusively involves stimulation of aqueous humor outflow. Bimatoprost appears to exert its effects on intraocular pressure by virtue of its inherent pharmacological activity as a prostamide. Bimatoprost is not a prodrug as it does not need to be converted to a free acid metabolite in the eye and no free acid was detected at the site of action in the eye.

Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.

Pharmacokinetics:

Bimatoprost penetrates the human cornea and sclera well in vitro. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean Cmax and AUC 0-24hrs values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steadystate was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 1/hr/kg.

Drug Substance Timolol maleate

Name (INN) : Timolol Maleate

Structural formula :

Molecular formula :
Molecular weight :
Chemical name

Mechanism of Action:
Timolol is a beta1 and beta2 non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing

aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Pharmacokinetics:
After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

Drug Product:
Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL, Preservative Free, Eye drops solution, multidose container is indicated in 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.