IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lataneau Plus 50 microgram/ml + 5 mg/ml Eye Drops, Solution
Timolol
Latanoprost
PA1608/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

I.1 Type of Application and aspects on development

This application for a new product authorisation has been made in accordance with Article 10(3) of Directive 2001/83/EC ("Hybrid Application"). The reference product has been licensed in the European Union for more than 8 years, but less than 10 years. As the innovator product has been authorised in the European Union for greater than 8 years, the applicant is not required to provide the results of pre-clinical and clinical trials. The majority of the evidence provided to support the clinical aspects of this application is therefore bibliographic in nature.

A biowaiver has been applied for by the applicant. This biowaiver application has been justified by the applicant as the medicinal products are essentially similar to the reference medicinal product, Xalcom, which is manufactured by Pfizer Ltd and has been authorised in the European Union since 2000. The products contain the same active ingredients as the reference product, in the same concentrations and in the same physical and dosage form.

Glaucoma is one of the leading causes of irreversible blindness worldwide, and treatment is aimed at reducing levels of intraocular pressure (IOP) using ocular hypotensive agents. Patients often need more than one class of IOP-reducing medication, and this can result in complex regimens which are difficult to maintain and can lead to non-compliance. Fixed-combination medicinal products can be helpful in reducing this complexity and improving compliance. Latanoprost/Timolol eye drop solution consists of two components, latanoprost and timolol maleate. Each mL of the solution contains latanoprost 50 microgrammes and timolol maleate 6.8mg, equivalent to 5mg timolol.

Latanoprost is a selective prostanoid FP receptor agonist, which reduces the IOP mainly by increasing the uveoscleral outflow of aqueous humour. Timolol is a non-selective beta-adrenergic receptor antagonist, and this class of drugs has until recently been the drugs of choice used to treat glaucoma. Timolol lowers the IOP by reducing the production of aqueous humour in the ciliary epithelium, although the precise mode of action is not clearly established.

It has been shown that the combination of these two active ingredients administered as a once-daily eye drop solution results in additional IOP reduction compared with either agent administered alone.

II. QUALITY ASPECTS

II.1 Introduction
Pharmaceutical form, formulation, container system, etc

II.2 2.2 Drug Substance
Drug substance Latanoprost

The drug substance latanoprost, is well established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.). The Active Substance Master File (ASMF) procedure is followed for the drug substance.

Synthesis of the drug substance has been satisfactorily described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient.

The active substance specification is considered adequate to control the quality and meets the current requirements. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

The container is suitable and provides adequate protection to the active substance.

Based on the stability data presented an appropriate re-test period has been set.

Drug substance Timolol Maleate

Timolol maleate is a well known active substance and it is monographed in the European Pharmacopoeia. The EDQM CEP procedure is used. The manufacturer of the drug substance timolol maleate has obtained a Certificate of suitability and the CEP is presented in the documentation.

The active substance specification is considered adequate to control the quality and meets the current requirements of the Ph. Eur. monograph for Timolol maleate and additional requirements as stated on the CEP. in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

The EDQM has approved a re-test period of 5 years if the material is stored in an inner PE bag in second Al/PE bag placed in fiber drum. This is stated in the CEP.

II.3 Medicinal Product

II.3.1 Composition

The Drug Product is presented as a combination product Latanoprost/Timolol as sterile, preserved, isotonic, multidose clear and colorless ophthalmic solution containing 50 mcg/ml of Latanoprost and 5mg/ml of timolol (as maleate) as active substances. It contains preservative benzalkonium chloride. The product is Low Density Polyethyelene (LDPE) primary packaging bottles equipped with a dropper applicator and a tamper evident cap, containing 2.5 ml of drug product in a cardboard box.

II.3.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The purpose of the development was to develop a stable product essentially similar to the reference product Xalacom. Comparative analysis with the reference product on the EEA Market demonstrated essential similarity.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques The manufacturing process has been validated using full scale batches. The results show good production performance throughout production. All tests meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

II.3.4 Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the relevant European guidelines and the standard requirements associated with eye preparations. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is presented in plastic bottles made of Low Density Polyethyelene (LDPE) equipped with a dropper applicator and a tamper evident cap, containing 2.5 ml of drug product in a cardboard box. *LDPE bottles are widely used for this type of product.* Bottle drawings and test certificates are provided. The packaging material complies with the relevant European guidelines.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage

conditions are stated in the Summary of Product Characteristics (SPC). Once open the product should be used within 4 weeks (see the SPC for further information).

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality ofLatanoprost + Timolol maleate Eye Drops Solution.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of latanoprost and timolol are well known. As both latanoprost and timolol are widely used, well-known active substances that have previously been extensively used in combination, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, considered appropriate.
The active principles used for the manufacturing of the proposed medicinal product Latanoprost/Timolol eyedrop solution, was introduced in 1996 in the US and Europe. Impurities and degradants are fully characterized and they do not exceed accepted standards.

As the medicinal product is a well established medicinal product with a similar composition compared to medicinal products already existing on the European market for many years and the product is intended to substitute for identical products on the market, the applicant indicates that approval of the above mentioned product will not result in increase of the total quantity of latanoprost or timolol released into the environment and will not result in increase of risk to the environment during use, storage and disposal. This statement is acceptable and no further environmental risk assessment is requested.

Discussion on the non-clinical aspects

As the innovator product has been authorised in the European Union for greater than 8 years, the applicant is not required to provide the results of pre-clinical studies. The majority of the evidence provided to support the preclinical safety is bibliographic in nature, and on review of this evidence the application is considered sufficient.

IV. CLINICAL ASPECTS

IV.1 CLINICAL PHARMACOLOGY
The clinical pharmacology of ocular Latanoprost and timolol is well established. The applicant has supplied bibliographic data to support the evaluation of the pharmacological profile of the active ingredients, and this is considered acceptable.

IV.2 CLINICAL EFFICACY
The clinical efficacy of this combination product is well established. Latanoprost is a selective prostanoid FP receptor agonist, which reduces the IOP mainly by increasing the uveoscleral outflow of aqueous humour. Timolol is a non-selective beta-adrenergic receptor antagonist, and this class of drugs has until recently been the drugs of choice used to treat glaucoma. Timolol lowers the IOP by reducing the production of aqueous humour in the ciliary epithelium, although the precise mode of action is not clearly established.
Literature references have been provided to support the demonstration of efficacy of the combination product over the individual components.

IV.3 CLINICAL SAFETY
The clinical safety of this combination product is well established. The product has been authorised and marketed in the European Union since 2000.The most common adverse event associated with Latanoprost is iris pigmentation, and this is more common in persons with mixed-colour irides, such as green-brown, yellow, brown, etc. It occurs very commonly, and while it generally occurs after prolonged use, it can occur after only a few months use. While there are no apparent adverse clinical effects of this hyper-pigmentation, it can be irreversible. Conjunctival and scleral hyperemia is also commonly observed. Latanoprost is not recommended in patients who have had ocular surgery.

As timolol is absorbed into the systemic circulation, it can cause adverse events in a similar way to other beta-adrenergic blocking agents. Patients with concomitant respiratory, cardiac, or endocrine diseases are generally advised to use beta-blockers with caution.

IV.4 Discussion on the clinical aspects

As the innovator product has been authorised in the European Union for greater than 8 years, the applicant is not required to provide the results of pre-clinical and clinical trials. The majority of the evidence provided to support the clinical aspects of this application is therefore bibliographic in nature, and on review of this evidence the application is considered sufficient from a clinical perspective.

IV.5 Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided

IV.6 Risk Management Plan

An EU-RMP was not considered necessary at this time – routine pharmacovigilance was deemed sufficient.

V. OVERALL CONCLUSIONS

Based on the information provided by the applicant, the risk/benefit profile of this fixed combination medicinal product appears to be positive.

VI. REVISION DATE

May 2011