IPAR

Public Assessment Report

Scientific discussion

Latanoprost/Timolol Zentiva 50 microgram/ml + 5 mg/ml Eye Drops Solution (Latanoprost)

IE/H/234/01/DC

Date: 17th May 2013

This module reflects the scientific discussion for the approval of Latanoprost/Timolol Zentiva 0,05mg/5mg/ml eye drops solution. The procedure was finalised at 17th May 2013. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Latanoprost/Timolol Zentiva 0.05/5 Mg/Ml Eye Drops Solution from Sanofi-aventis Ireland Limited

The product is indicated for the treatment of open angle glaucoma and ocular hypertension.

A comprehensive description of the indications and posology is given in the SmPC.

“The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC (“Hybrid Application”)

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.

II QUALITY ASPECTS

II.1 Introduction

This application is for Latanoprost and Timolol 50 microgram/ml + 5 mg/ml, Eye Drops Solution.

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. 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 packaged in Low Density Polyethyelene (LDPE) 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 of Latanoprost/Timolol Zentiva 50 microgram/ml + 5mg/ml Eye Drops Solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

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. The product is intended to substitute for identical products on the market.
The 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.

III.2 Ecotoxicity/environmental risk assessment (ERA)

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.

III.3 Discussion on the 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.

IV CLINICAL ASPECTS

IV.1 Pharmacokinetics / Pharmacodynamics

The clinical pharmacology of Latanoprost and timolol are well established, and has been described by the literature references provided in the dossier by the applicant.

Latanoprost is a prostanoid selective FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. In addition, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost is a pro-drug, and is hydrolysed during its passage through the cornea to form the active acid. Latanoprost undergoes practically no metabolism in the eye, but is converted to 1,2 dinor and 1,2,3,4 tetranor metabolites in the liver, which are then excreted in the urine.

Timolol maleate 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-stabilizing) activity. Timolol lowers the IOP by decreasing the formation of aqueous humour in the ciliary epithelium. The precise mechanism of

action is not clearly established. Timolol has been shown to provide excellent additivity with other ocular hypotensive agents. Timolol is extensively metabolised by hydrolysis in the liver.

IV.2 Clinical efficacy

The clinical efficacy of Latanoprost and timolol, both individually and in this fixed combination is well established, however the absence of a therapeutic equivalence study is noted and should be further clarified by the applicant. The clinical efficacy of the fixed combination product has been described in the literature references provided by the applicant.

In clinical trials, the administration of Latanoprost and timolol in combination reduced the IOL in affected eyes to a greater degree than seen with either agent used individually. The effect was maintained in long-terrn studies.

IV.3 Clinical safety

The safety profile of the active ingredients is well known. 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

The clinical pharmacology of ocular Latanoprost and timolol is well established; as such, the applicant has supplied bibliographic data to support the evaluation of the pharmacological profile of the active ingredients. These references were sufficient in the context of this application to support the granting of a marketing authorisation for this product for these indications.

V OVERALL CONCLUSIONS

Following the assessment of the application for marketing authorisation, the Member States are in agreement that the benefit-risk profile of the product is positive. As such, a marketing authorisation can be granted.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59 (3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI REVISION DATE

May 2013