IPAR

Public Assessment Report

Scientific discussion

Latacris 50 microgram/ml Eye Drops, Solution (Latanoprost)

IE/H/216/01/DC

Applicant: PH&T S.p.A.

This module reflects the scientific discussion for the approval of Latacris 50 microgram/ml Eye Drops, Solution. The procedure was finalised at 26th April 2011. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

I.1 About the product

Latacris 50 microgram/ml eye drops solution contains latanoprost, a prostaglandin analogue. Latanoprost reduces the intraocular pressure (IOP) by increasing the outflow of aqueous humour, mainly through the uveoscleral pathway and trabecular meshwork.

I.2 General comments on the submitted dossier

This application is being made in accordance with Article 10(3) of Directive 2001/83/EC, a “hybrid” application. The reference product is Xalatan, a medicinal product which has been authorised in a number of European Member States since 1996. The applicant has submitted a clinical study designed to demonstrate therapeutic equivalence with the above mentioned reference product.
The reference product used in this application has been authorised in the European Union for more than 10 years. The legal basis for this application is acceptable, as are the proposed indications for use.
The active substance is not considered a new active substance.

I.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these types of product at the site responsible for the batch release, manufacture and assembly of this product.

For the manufacturing site within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The Qualified Person of the manufacturer, who is located in the EEA and who is responsible for batch release in the EEA, has declared that the active substance manufacturers operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.

II QUALITY ASPECTS

II.1 Introduction

This application is for Latacris 50 microgram/ml eye drops solution.

II.2 2.2 Drug Substance

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.

II.3 Medicinal Product

II.3.1 Composition

The Drug Product is presented as a sterile, preserved, isotonic, multidose clear and colorless ophthalmic solution containing 50 microgram/ml of Latanoprost as active substances. It contains preservative benzalkonium chloride. The product is packaged in bottles made of High Density Polyethyelene (HDPE)/Low Density Polyethyelene (LDPE) and equipped with a dropper applicator and a screw 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 Xalatan. 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 High Density Polyethyelene (HDPE)/Low Density Polyethyelene (LDPE) equipped with a dropper applicator and a screw cap, containing 2.5 ml of drug product in a cardboard box. HDPE/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 Latacris 50 microgram/ml eye drops

solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

Latacris 50 microgram/ml eye drops solution is indicated for the treatment of open angle glaucoma (ATC: S 01 E E 01). The legal basis for this application is an abridged application according to Art 10.3 of Directive 2001/83/EC as amended. According to Directive 2001/83/EC as amended, the applicant is not required to provide the results of pre-clinical tests and clinical trials if the product is the generic of a reference medicinal product. For this reason no pre-clinical studies specifically designed to assess the pharmacodynamics and pharmacokinetics of Latacris 50 microgram/ml eye drops solution was performed. The safety of the product was however explored, by means of a non-clinical study on the local tolerability in rabbits.
The non-clinical overview fulfils the obligations as set out in article 12, and in accordance with annex I, part I 1.4 of Directive 2001/83/EC, as amended.
As the medicinal product is a well-established medicinal product with a similar composition to medicinal products already existing on the European market for many years and the product is intended to be a substitute for identical products on the market, the applicant states that approval of the above mentioned product will not result in increase of the total quantity of latanoprost 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.
A single local tolerability study was performed comparing Lactacris with the reference product Xalatan. This study was performed in compliance with good laboratory practice (GLP) and is considered acceptable to support the application.

III.2 Pharmacology

The pharmacology of latanoprost is well known and documented within the literature and as such new studies have not been submitted. The reviewer has provided an extensive historical and scientific overview of the available literature data with respect development of latanoprost as well as the *in vitro* and *in vivo* studies in a number of species, outlining the pharmacology and mechanism of action of latanoprost. The reviewer has provided an overview of the available literature data with respect to the pharmacokinetics of latanoprost.

III.3 Pharmacokinetics

III.4 Toxicology

Latanoprost has been used extensively and the toxicological profile is considered to be well established. A sufficient overview of the available toxicological data, with respect to topical repeat dose studies, reproductive toxicology, genotoxicity and carcinogenic potential has been provided.

A new special ocular tolerability study was performed and presented comparing Latacris 50 microgram/ml eye drops solution with that of the originator (Xalatan). The study was performed according to GLP.
Ocular irritation and/or corrosion following instillation of test item into the eye of the rabbit were evaluated by grading of any ocular irritation reactions seen, using a predetermined scoring system in accordance with the general requirements of OECD guidelines No. 405., and inspired by the EMEA note of the Committee on Medicinal Products for guidance on clinical local tolerance testing (CPMP/SWP/2145/00) adapted March 1, 2001.

Ophthalmological examination (retinography) was performed on all animals at pre-treatment and once a week from D1 to D28.
No abnormalities or causes of concern were identified in animals treated with Latacris 50 microgram/ml eye drops solution or with Xalatan eye drops. There were no treatment-related changes.
In conclusion, under the experimental conditions adopted, Latacris 50 microgram/ml eye drops solution or Xalatan, administered in the conjunctival sac of the left eye of the rabbit for 28 consecutive days, did not show clinical signs and/or local ocular lesions, except a slight redness of conjunctiva in 1/6 animals treated with Xalatan eye drops on D22.

III.5 Ecotoxicity/environmental risk assessment

No environmental risk assessment has been performed or is required.

III.6 Discussion on the non-clinical aspects

Latanoprost is a well established active used in the treatment of open angle glaucoma, it pharmacology and safety are considered to be well known and understood. The applicant has performed a single toxicological study to investigate potential effects of Lactacris in the eye and found no cause for concern in line with the established safety profile of latanoprost.

IV CLINICAL ASPECTS

Clinical pharmacology

The clinical pharmacology of latanoprost is well established. No clinical pharmacology studies have been submitted in support of this application, and none are required.

Clinical efficacy

A single therapeutic equivalence study has been submitted in support of his application.

The study was a multi-centre, prospective randomised double-blind, parallel-group comparison study in patients with known glaucoma or intraocular hypertension requiring treatment. The primary end-point was the change in intraocular pressure (IOP) from baseline in the two study groups at 12 weeks. One hundred and ninety-six subjects were screened and one hundred and eighty-five randomized in the 6 investigational centres. The target to be reached, according to the sample size calculation, was one hundred sixty eight completed subjects.

At baseline, mean intraocular pressure (IOP) levels were similar across groups at each time point and for diurnal measurement. With regard to the primary efficacy variable, mean intraocular pressure level (9:00, 13:00 and 17:00) at baseline was 22.8 mm Hg in both treatment groups. By week 12 a significant ($p<.001$) reduction was observed in both treatment groups (16.4 mm Hg in both groups). The least-squares mean (95% confidence interval) was -6.24 mm Hg (-6.66 - -5.82) for latanoprost treated patients and -6.36 mm Hg (-6.77 - -5.94) for the Xalatan-treated patients. Treatment difference was 0.12 mm Hg and 95 % confidence interval -0.47 - + 0.71. Results of per-protocol analyses of changes from baseline to week 12 in mean intraocular pressure levels were supportive of those of the intention-to-treat evaluations. Least-squares mean (95% confidence interval) was -6.41 mm Hg (-6.82 - -5.99) for the latanoprost treated patients and -6.40 mm Hg (-6.80 - 6.00) for the Xalatan-treated patients. Treatment difference was 0.00 mm Hg and 95 % confidence interval -0.58 - + 0.57.

Therapeutic equivalence is therefore considered to have been demonstrated.

Clinical safety

The number of patients with at least one drug-related adverse event was 21 (22.8%) in the latanoprost group and 12 (12.9%) in the Xalatan group. The difference between groups was not significant (chi-square test p-value = 0.0.78).
The total number of serious adverse events during the treatment period was 2, both reported by one patient (1.1%) in the latanoprost group. The difference between groups was not significant (Fisher exact test p-value = 0.497).
The total number of adverse events leading to withdrawal during the treatment period was 1 in the latanoprost group and 3 in the Xalatan group. The number of patients with at least one adverse event leading to withdrawal during the treatment period was 1 (1.1%) in the latanoprost group and 1 (1.1%) in the Xalatan group. The difference between groups was not significant (Fisher exact test p-value = 1.000).
There were no substantial differences between groups in the results of the other safety endpoints (laboratory tests, physical examination findings, vital signs and local tolerability variables).

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.

Risk Management Plan

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

V OVERALL CONCLUSIONS

As this is a generic application, additional studies are not necessary. Therapeutic equivalence has been demonstrated between the test and reference products, as described above. As such, the benefit-risk profile of this product is positive.

VI REVISION DATE

August 2011