CBG MEB

Public Assessment Report

Scientific discussion

Latanostad 50 microgram/ml eye drops, solution

(latanoprost)

NL/H/3195/001/DC

Date: 8 December 2016

This module reflects the scientific discussion for the approval of Latanostad 50 microgram/ml eye drops, solution. The procedure was finalised on 16 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Latanostad 50 microgram/ml eye drops, solution from Stada Arzneimittel AG.

The product is indicated for:

- reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension
- reduction of elevated intraocular pressure in paediatric patients with elevated pressure and paediatric glaucoma.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Xalatan, eye drops 50 microgram/ml (NL License RVG 21304) which has been registered in the Netherlands by Pfizer B.V. since 10 June 1997 through MRP UK/H/0179/001.

The concerned member state (CMS) involved in this procedure was Czech Republic.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated trough bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Latanostad 50 microgram/ml is a clear colourless solution, free of visible particulate matter, with a pH between 6.4 and 7.0 and a osmolality of 240-290 mOsm/kg.
One ml eye drops solution contains 50 micrograms of latanoprost and one drop contains approximately 1.5 microgram latanoprost.

The solution is packed in a clear LDPE bottle with a clear LDPE dropper tip and a white HDPE cap with a tamper evident mechanism. The fill volume of a multiple dose unit is 2.5 ml and provides approximately 80 droplets of drug product.

The excipients are: benzalkonium chloride, sodium dihydrogen phosphate monohydrate (E339), disodium hydrogen phosphate anhydrous (E339), sodium chloride and purified water.

II.2 Drug Substance

The active substance is latanoprost, a well known active substance, however not described in any pharmacopoeia. It is a colourless to yellow viscous liquid without visible contaminants and practically insoluble in water.Latanoprost does not exhibit polymorphism. The drug substance contains five chiral centres. The 15R-isomer is the active isomer.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The active substance has been manufactured in accordance with the detailed Guideline on good manufacturing practice for active substances used as starting materials as required by Article 46(f) of Directive 2001/83/EC as amended by Directive 2004/27/EC. The proposed starting materials are acceptable as start of synthesis. Sufficient data have been provided.

Quality control of drug substance
The active substance specification has been established in-house and is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three small sized batches and one large sized batch.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches of the small batch size stored in accordance with applicable European guidelines for 24-36 months at -15°C ± 5°C and 6 months stored at 5°C ± 3°C.
Based on the data submitted, a retest period could be granted of 24 months with the storage condition: “store in freezer (-10°C to -20°C) and keep the vial in the outer bag in order to protect from light”.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Sterilisation is performed by sterile filtration. The drug substance is known to be practically insoluble in water and also adheres to certain plastics from the solution. The main development studies performed are in relation to the preparation of a homogeneous latanoprost solution, suitability testing of the sterilising filter, adhesion studies in order to optimize materials used during manufacture and selection of a suitable package. The choice of the packaging and manufacturing process are justified.
No bioequivalence study has been conducted. The qualitative composition of the test and reference product is similar. The MAH provided comparative data for colour, pH, surface tension, specific gravity, viscosity and osmolality for three batches of the test and reference product. Based on the composition of test and reference product and the demonstration of pharmaceutical similarity, bioequivalence studies are waived.

Manufacturing process
The main steps of the manufacturing process are the compounding of the excipients and the active substance into a homogeneous solution, after which the solution is filtrated through a sterilisation filter and filled into the primary container closure system.. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot scale batches and 3 full scale batches.

Control of excipients
The excipients comply with the requirements of the pharmacopoeia. These specifications are acceptable.

Microbiological attributes
Latanoprost ophthalmic solution is a sterile solution and contains 0.02 mg/ml benzalkonium chloride (BAC) as a preserving agent, which is a common concentration for ophthalmic solutions. Preservative effectiveness after 24 months (including 6 weeks of in-use) was confirmed for two batches. Furthermore, preservative effectiveness was performed for 100%, 80% and 60% of the benzalkoniumchloride levels included in the drug product. Results show that the latanoprost solution is effectively preserved even at 60% of the initial benzalkonium content. The 0.2 mg/ml BAC is justified as the innovator uses the same concentration.

Quality control of drug product
The product specification includes tests for appearance, identification, assay, uniformity of dosage units, pH, deliverable volume, sterility, osmolality, particulate matter, degradation products, number of droplets per bottle, leakage of container, weight loss and antimicrobial effectiveness. The release and

shelf-life requirements and limits are identical and acceptable in accordance with the various European guidelines, except for impurities. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on 3 pilot scaled and 3 full scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for 3 pilot scale and 3 full scale batches in accordance with applicable European guidelines. The data cover 12 months for the pilot scale batches and 9 months for the full scale batches stored at 2 - 8°C. Both batch sizes were stored for 6 months at 25°C/60% RH. The batches were stored in LDPE containers with LDPE dropper inserts and HDPE caps. Based on the results, a shelf-life of 24 months for the product stored in a refrigerator (2 - 8°C) was granted.

No formal photostability study data was included. During forced degradation studies latanoprost ophthalmic solution is shown to be instable to UV exposure. The proposed storage condition protected from light is therefore acceptable without further photostability studies performed.

Also data of a 4-week in-use stability study have been provided. Antimicrobial effectiveness after 4 weeks in-use conforms with the specifications. No significant increases of degradation products are observed. After first opening the product may be stored for 4 weeks at conditions at or below 25°C. During in-use storage the product is also to be kept in the outer carton in order to protect the product from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Latanostad has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The starting material has been adequately defined and specified, in accordance with the current guidelines.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Latanostad is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Xalatan 50 microgram/ml eye drops, solution which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Latanoprost is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

According to the Guideline on Investigation of Bioequivalence, a waiver of clinical studies for locally acting locally applied drug products is acceptable in the case of solutions, e.g. eye drops. No comparative clinical study to show therapeutic equivalence between the hybrid product and the reference product has been conducted. Based on the qualitative and quantitative composition of test and reference product, which only show a minor difference, clinical therapeutic equivalence studies may be waived based on demonstration of pharmaceutical similarity.
Thus the requirements are fulfilled for locally applied, locally acting products under the EU CPMP guideline on bioequivalence (CPMP/EWP/239/95). Latanostad 50 microgram/ml eye drops, solution may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Latanostad.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Conjunctival hyperaemia • Eye lash and vellus hair changes • Periorbital skin discoloration • Iris hyperpigmentation
Important potential risks	• Cystoid macular oedema • Aggravation of asthma • Ocular and cutaneous melanoma
Missing information	• Ocular tolerability in paediatric population • Long-term safety in paediatric patients (including ocular hyperpigmentation and neurodegenerative events; hyperpigmentation changes in the eye, and corneal endothelial function/corneal thickness) • Drug interactions in adult and paediatric patients • Use in pregnant and lactating women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

Post approval the MAH should perform literature searches to provide information on “background incidence/prevalence”, “risk groups or risk factors” and “potential mechanism” for inclusion in the RMP, as this information is incomplete. For the item “preventability”, the MAH should consider providing information to patients, and/or monitoring of the clinical situation and if needed discontinuation of latanoprost.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xalatan. No new clinical studies were conducted. The MAH demonstrated pharmaceutical

equivalence to the reference product based on *in vitro* data. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. 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. After a pilot test with three subject a test with 20 test subjects was started. The two objectives of this test was to check whether the information was found and whether the information was understood. All results were evaluated by statistical methods. Contingency tables were used to analyse the individual difficulties in finding information and answering the questions correctly. 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 product for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Latanostad 50 microgram/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Xalatan, eye drops 50 microgram/ml, a well-known medicinal product with an established favourable efficacy and safety profile.

As Latanostad is a product for ocular use (eye drops) intended to act without systemic absorption, with the same excipients used in the reference product, it is exempted for bioequivalence study.

During the assessment procedure, the MAH was asked to redefine the starting material in accordance with the current guidelines. A revised definition, specifications and description of the route of synthesis were submitted; these were discussed in the Board meeting of 4 June 2015. The starting material has been adequately redefined.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Latanostad 50 microgram/ml eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 June 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached