

Public Assessment Report

Scientific discussion

**Latanoprost Horus Pharma 0.05 mg/ml eye
drops, solution in unit dose container**

(latanoprost)

NL/H/3593/001/DC

Date: 16 October 2017

This module reflects the scientific discussion for the approval of Latanoprost Horus Pharma 0.05 mg/ml eye drops, solution in unit dose container. The procedure was finalised on 18 January 2017. 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
BAK	Benzalkonium Chloride
BP	British Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IOP	Intraocular Pressure
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Latanoprost Horus Pharma 0.05 mg/ml eye drops, solution in unit dose container from Horus Pharma.

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 intraocular pressure and paediatric glaucoma.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xalatan 50 microgram/ml eye drops which has been registered in the United Kingdom by Pfizer Limited since 16 December 1996. In the Netherlands Xalatan, eye drops 50 microgram/ml (NL License RVG 21304) has been registered since 10 June 1997 through a mutual recognition procedure (UK/H/0179/001).

The concerned member states (CMS) involved in this procedure were Belgium, Luxembourg and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Latanoprost Horus Pharma eye drops, solution is a clear colourless liquid with a pH of approximately 6.7 and osmolality of approximately 280 mOsm Kg⁻¹.

One ml of solution contains 50 micrograms of latanoprost and one drop contains 1.5 micrograms of latanoprost.

The solution is packed in unit dose containers (0.2 ml) of low density polyethylene without additives, slightly opaque and thermally sealed.

The excipients are: sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, sodium chloride and water for injection.

II.2 Drug Substance

The active substance is latanoprost, an established active substance that is not described in the European or British Pharmacopoeia (Ph.Eur.; BP). Latanoprost is a colourless to yellow viscous oil, free from visible particles. The drug substance is practically insoluble in water, but soluble at the concentration used in the formulation. The active substance is a single enantiomer. Polymorphism is not considered relevant as the intended drug product is a solution.

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 manufacturing process consists of twelve steps. No class 1 organic solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 12 full scale batches.

Stability of drug substance

Stability data are provided on active substance of ten batches stored at -20°C (4 batches for 24 months; 2 batches for 36 months; 1 batch for 9 months), 2°C-8°C (2 batches for 36 months; 1 batch for 10 months; 1 batch for 9 months) and 25°C/60% RH (8 batches for 6 months). At all three storage conditions no changes or trends are seen, with the exception of one batch stored at 2°C-8°C. Consequently adequate preventive actions have been implemented with the manufacture of all post-validation batches.

The currently acceptable retest period is 24 months when protected from light and stored in a freezer (-20°C) is justified.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients, packaging and manufacturing is justified. The overage is also justified. The main development studies concerned the characterisation of the reference product and the development of the manufacturing process. The product contains the same concentrations of latanoprost and the same qualitative composition with the exception of the preservative benzalkonium chloride (BAK). The drop size of the product delivered with the selected dropper for the test product is comparable to that for the reference product. Viscosity is also comparable. The physicochemical characteristics are similar to the innovator, except for the surface tension. It is sufficiently justified that the two differences (composition and surface tension) are not clinically relevant. Similarity has adequately been demonstrated.

The choice of the sterilisation method (filtration in combination with aseptic processing) was selected in accordance with the decision tree for sterilisation choices for aqueous product (Annex to the Note for Guidance on Development Pharmaceuticals)

Manufacturing process

The manufacturing process consists of the preparation of the solution, aseptic filtering and filling aseptically in unit dose containers. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for at least three production scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the requirements of the Ph.Eur. or United States Pharmacopoeia (USP). These specifications are acceptable.

Microbiological attributes

The drug product is routinely tested for sterility. This is in line with the requirements for eye drops solutions of the general Ph.Eur. eye preparations monograph. Sterility requirements for drug products are granted by sterile filtration of the bulk, by aseptic filling and by the use of unit dose sterile containers.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, density, uniformity of dosage units, extractable volume, osmolality, identification, related substances, assay, sterility, particulate matter

and visible particles. Except for related substances, the release and shelf-life requirements/limits are identical. The specification is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from at least three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three production scale batches stored at 2-8°C (36 months) and 25°C/60% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed unit dose containers. All parameters remain within the specified limits. Photostability data did not show change of latanoprost assay or impurities. The proposed shelf-life of 36 months and storage conditions 'Store in a refrigerator' are justified.

Stability data has been provided demonstrating that the product remains stable for seven days following opening of the pouch, when stored below 25°C.

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 Latanoprost Horus Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made:

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Latanoprost Horus Pharma is intended for generic 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 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.

No clinical studies were submitted to support the application. The MAH claims a biowaiver based on the following: the same qualitative and quantitative composition in terms of active principles, and the same pharmaceutical form. The overview justifies why there is no need to generate additional clinical data. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The request for a biowaiver has been made with a reference to the NfG on Investigation of Bioequivalence, Appendix II, Locally acting, locally applied products. According to the guideline, in case of solutions, such as eye drops, a biowaiver may be acceptable, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties of the test product and reference product are identical or essentially similar. Any qualitative or quantitative differences in excipients must be satisfactorily justified in relation to their influence on therapeutic equivalence.

The physicochemical characteristics are similar to the innovator, except for the surface tension. Both the drop size and the drop weight are highly similar between Xalatan and the generic latanoprost solutions. For a lipophilic drug like latanoprost, difference in surface tension is considered not to be clinically relevant, in contrast to hydrophilic drugs. Transcellular permeation of lipophilic drugs through the cornea is faster and greater as compared to hydrophilic drugs. This entails that a substance that enhances the absorption of certain drugs, like a preservative, is not needed for a lipophilic drug, such as latanoprost. A lipophilic substance does not need the presence of a surface-active agent in order to remain in the epithelium and to be absorbed into the corneal stroma. Reference is also made to several studies on the intraocular pressure (IOP) reduction of other prostaglandins (e.g. bimatoprost, tafluprost, travoprost), where a direct comparison was made between formulations with and without preservative BAK. These data provide evidence that BAK is not required for IOP reduction, at least not with the class of prostaglandins, being lipophilic drugs. As the efficacy of the prostaglandins in patients with open angle glaucoma or ocular hypertension was not influenced by the presence or absence of BAK, and no further clinical studies are required to conform this. From safety perspective the absence of BAK is also considered favourable, as patients may be intolerant to BAK.

Based on the above, the two formulations are considered equivalent with regard to efficacy and safety. A waiver for clinical studies is considered justified.

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 Latanoprost Horus Pharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> • Conjunctival hyperaemia • Eyelash and vellus hair changes • Periorbital skin discoloration • Iris hyperpigmentation • Keratitis herpetic
Important potential risks	<ul style="list-style-type: none"> • Cystoid macular oedema • Aggravation of asthma • Ocular and cutaneous melanoma
Missing information	<ul style="list-style-type: none"> • Ocular tolerability in paediatric population

	<ul style="list-style-type: none"> • Long-term safety in paediatric population (including ocular developmental 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
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xalatan. It is accepted that no new clinical and bioequivalence studies were conducted, while a biowaiver was granted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Latanoprost Horus Pharma 0.05 mg/ml eye drops, solution in unit dose container has a proven chemical-pharmaceutical quality and is a generic form of Xalatan 50 microgram/ml eye drops. Xalatan is a well-known medicinal product with an established favourable efficacy and safety profile.

Latanoprost Horus Pharma is a preservative free product for ocular use (eye drops) intended to act without systemic absorption. In contrast to the innovator product, Latanoprost Horus Pharma does not contain the preservative benzalkonium chloride. Chemical-physical properties are shown to be similar to Xalatan, except for the surface tension. The MAH has provided sufficient documentation and argumentation to show that the difference in surface tension between Xalatan and Latanoprost Horus Pharma is not considered clinically relevant. The two formulations are considered equivalent with regard to efficacy and safety and therefore no clinical studies are required.

The Board followed the advice of the assessors.

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 Latanoprost Horus Pharma 0.05 mg/ml eye drops, solution in unit dose container with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 January 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)