CBG MEB

Public Assessment Report

Scientific discussion

Xalmono 0.05 mg/ml eye drops, solution in unit dose container

(latanoprost)

NL/H/3193/001/DC

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This module reflects the scientific discussion for the approval of Xalmono 0.05 mg/ml eye drops, solution in unit dose container. The procedure was finalised on 27 November 2014. 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 Xalmono 0.05 mg/ml eye drops, solution in unit dose container, from Genetic S.p.A.

The product is indicated for the treatment of:

- 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 hybrid application claiming essential similarity with the innovator product Xalatan 0.005% eye drops solution which has been registered in the United Kingdom by Pfizer Limited, UK since 1996 (original product). In the Netherlands, Xalatan (NL license RVG 21304) has been registered since 1997 by the procedure UK/H/0179/001/MR.

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

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Xalmono is an eye drop solution packed in single dose containers and contains as active substance 0.05 mg/ml of latanoprost, The solution is a clear colourless liquid with a pH of approximately 6.7 and osmolality of approximately 280 mOsm/Kg.
One ml eye drops solution contains 50 micrograms of latanoprost. One drop contains approximately 1.5 micrograms latanoprost, which is similar to the reference product. Each single dose container has 0.2 ml eye drops, packed in thermally sealed low density polyethylene without additives. Five unit dose containers are contained in a pouch of PET/Al/PE. The pouch is inserted in a carton box.

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 described in the US Pharmacopoeia (USP). The active substance is a colourless to yellow viscous oil, practically insoluble in water. Latanoprost has five chiral centres; the active substance is a single enantiomer.

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 is divided into twelve steps. No class 1 organic solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for solvents and reagents.

Quality control of drug substance
The drug substance specification of the ASMF holder has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 10 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for batches stored at -20°C (three batches, 24 months), 2-8°C (3 batches, up to 36 months) and 25°C/60% RH (six batches, 6 months). At all three storage conditions, elevated (25°C/60% RH), accelerated (2-8°C) and long-term (-20°C), no changes or trends are seen, with the exception of one batch stored at 2-8°C. 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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies regarded the characterisation of the reference product to obtain a homogenous solution essentially similar to Xalatan and the development of the manufacturing process. The choices of the packaging and manufacturing process are justified. The solution is sterilised by sterile filtration. The pharmaceutical development of the product has been adequately performed. The MAH has demonstrated that the drop size of both test and reference product are comparable (about 30 µL per drop). Xalatan contains benzalkonium chloride (BAK) as a preservative in contrast to Xalmono, which is a preservative free solution. The physicochemical characteristics including viscosity and density are similar to the innovator, except for the surface tension. The product displays a higher value than the reference product due to the absence of the cationic surfactant BAK. However, this difference in surface tension between the drug product and the reference product has been justified sufficiently by supporting data and is considered to be not clinically relevant.

Manufacturing process
The manufacturing process consists of the preparation of the solution, aseptic filtering and filling in unit dose containers. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches.
In the manufacturing process an overage of 5% of latanoprost is used to compensate losses due to adsorption. This overage has been adequately justified.

Control of excipients
The excipients comply with the requirements of the Ph.Eur. or USP. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance (clarity and colouration), pH, density, uniformity of dosage units, extractable volume, osmolality, identification, related substances, assay, sterility and particulate matter. Except for related substances, the release and shelf-life requirements/limits are identical.
The specification is considered to be acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Microbiological attributes
Xalmono 0.05 mg/ml, eye drops, solution in unit dose containers, is sterile and in compliance with prescriptions for category 1 of Ph. Eur. 5.1.4. Controls are performed according to the monograph Ph. Eur. 2.6.1. Sterility requirements for drug products are granted by sterile filtration of the bulk, by

aseptic filling and by the use of sterile unit dose containers. In the formulation, excipients with a specific antimicrobial activity are not present. Therefore the unit dose container must be discarded after single use.

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 (6 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.
At both storage conditions an increase of an impurity is observed. No further changes are seen and all parameters remain with the specified limits. The proposed shelf-life of 36 months and storage condition 'Store in a refrigerator' are justified. Photostability tests performed on naked strips and pouched strips in the box of the drug product showed that the product is not sensitive to light.
Stability data has been provided demonstrating that the product remains stable for 7 days following opening of the pouch, when stored below 25°C. As the product is a preservative free formulation, an in-use period after opening is not acceptable. The container should be opened immediately before use and disposed after use.

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 Xalmono 0.05 mg/ml, eye drops, solution in unit dose containers has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment has been made:

- The MAH committed to monitor the progress of validation of the first steps of the synthesis of the active substance latanoprost to further confirm GMP compliance.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Xalmono 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 eye drops 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 Xalmono 0.05 mg/ml eye drops.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Conjunctival hyperaemia • Eyelashes 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 population • Interactions in paediatric patients • Limited experience with patients with asthma

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 0.005% eye drops solution. No new clinical studies were conducted. The product can

be considered essentially similar to the reference product based on chemical-pharmaceutical properties. 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 language used for the purpose of user testing the PL was English.
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.
The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The participants tested were between 18 and 70 years of age, with variable education level, male as well as female. Before the start of the user test, the PL was reviewed and further improved. Diagnostic testing was performed. Questions (15 in total) were asked about all parts of the leaflet, covering the areas traceability, comprehensibility and applicability. Additionally 4 general questions about layout and to obtain feedback were formulated. After the pilot test, as well as after the first round with 10 participants, no amendments of the PIL were considered necessary. Overall, each question meets the criterion of 81% correct answers. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xalmono 0.05 mg/ml eye drops, solution in unit dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Xalatan 0.005% eye drops solution. Xalatan is a well-known medicinal product with an established favourable efficacy and safety profile

Xalmono 0.05 mg/ml is a preservative free product for ocular use (eye drops) intended to act without systemic absorption. In contrast to the innovator product, Xalmono 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 Xalmono is not considered clinically relevant. The two formulations may be 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 Xalmono 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 27 November 2014.

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
NL/H/3193/ 1/IA/002	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System master File (PSMF) location	--	1-12-2015	Non-approval	
NL/H/3193/ 1/IB/001	The MAH wishes to introduce a new name due to a transfer MAH from Pharmaceutical Works Polpharma SA to Genetic S.P.A. in The Netherlands.		13-1-2016	Approval	
NL/H/3193/ 1/IA/003	Introduce the summary of the PSMF of GENETIC S.P.A		29-3-2016	Approval	
NL/H/3193/ 1/IB/004	Request to vary the Marketing Authorisation detailed in the application		27-6-2016	Approval	
NL/H/3193/ 1/IB/005	Request to vary the Marketing Authorisation detailed in the application		27-6-2016	Approval	

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