CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Eylasol 50 µg/ml, eye drops, solution
Premier Research GmbH, Germany

latanoprost

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1406/001/DC
Registration number in the Netherlands: RVG 102637

25 August 2010

Pharmacotherapeutic group:	antiglaucoma preparations and miotics, prostaglandin analogues
ATC code:	S01EE01
Route of administration:	ocular
Therapeutic indication:	reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.
Prescription status:	prescription only
Date of authorisation in NL:	16 July 2010
Concerned Member States:	Decentralised procedure with ES, IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Eylasol 50 µg/ml, eye drops, solution from Premier Research GmbH. The date of authorisation was on 16 July 2010 in the Netherlands.
The product is indicated for reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.

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

The active substance latanoprost, a prostaglandin $F_{2\alpha}$analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xalatan 50 µg/ml eye drops which has been registered in the United Kingdom by Pfizer since 16 December 1996. The UK acted as RMS in the subsequent MRP (UK/H/0179/001). In the Netherlands, Xalatan 50 µg/ml (NL License RVG 21304) has been registered since 10 June 1997. In addition, reference is made to Xalatan authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Eylasol 50 µg/ml is a product for ocular use (eye drops) intended to act without systemic absorption, with qualitatively and quantitatively the same excipients used in the reference product, it is exempted for biostudy (Guideline CPMP/239/95 on locally applied, locally acting products, containing known constituents). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is latanoprost, an established active substance, however not described in the European, British or US Pharmacopoeia (Ph.Eur.*). The active substance is a colourless to yellow viscous oil, which is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water. Latanoprost does not exhibit polymorphism. Latanoprost 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 manufacturing process consists of 9 steps, with several intermediates and starts with two starting compounds. During the process, several purification steps are used to finally produce the latanoprost drug substance. No class 1 organic solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house; the specification is considered acceptable in view of the route of synthesis and the various European guidelines. For water content the specifications might be tightened as additional batches are manufactured. Batch analytical data demonstrating compliance with the drug substance specification have been provided for eight pilot-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three pilot-scale batches stored at -20°C ± 5°C (24 months) and 5°C ± 3°C (24 months). The batches were adequately stored. Under both conditions, no changes are observed within the proposed retest period of 12 months. Therefore, the proposed retest period of 12 months and storage condition (-20°C) were granted.

** Ph.Eur., USP and BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Eylasol 50 µg/ml is a clear, colourless liquid with pH 6.4-7.0 and osmolality 240-290 mOsm/kg.

One ml eye drops solution contains 50 micrograms of latanoprost. One drop contains approximately 1.5 micrograms latanoprost.

The solution is packed in LDPE bottles with HDPE screw cap. Each bottle contains 2.5 ml eye drops solution corresponding to approximately 80 drops of solution.

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

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 adhere 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.
The qualitative formulation of this product is identical to the innovator. In order to show equivalence of the product to the originator product, several physiochemical and content parameters of the originator products from the concerned member states have been compared with the drug product at issue. The MAH has shown that critical parameters, e.g., viscosity, surface tension and drop size are similar to the innovator product. Equivalence was adequately shown. The pharmaceutical development of the product has been adequately performed.

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.

Container closure system

Sterilisation is conducted by gamma radiation and complies with the minimum absorbed dose of radiation as described in Ph.Eur. The effectiveness of the irradiation process itself and the variation of irradiation dose at different spots throughout the irradiation chamber have been evaluated.

Microbiological attributes

Latanoprost eye drops is a sterile solution and contains 0.02 mg/ml benzalkoniumchloride (BAC) as a preserving agent, which is a common concentration for ophthalmic solutions. Preservative effectiveness study is performed at BAC levels of 100%, 80% and 60% inoculated with bacteria using pharmacopoeial methods. Results show that latanoprost ophthalmic solution is effectively preserved even at BAC levels as low as 60%. 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/limits are identical and are acceptable in accordance with the various European guidelines. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on 3 pilot-scale and 3 full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided 3 pilot-scale batches stored at 2-8°C (12 months) and 25°C/60% RH (6 months) and 3 full-scale batches stored at 2-8°C (9 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 LDPE containers with LDPE dropper inserts and HDPE caps. During storage at

accelerated conditions (25°C/60% RH) within 3 months a significant change in latanoprost assay is observed (> 5%). The proposed shelf-life of 12 months for the product stored in a refrigerator (2-8°C) could be granted. Also stability data has been provided demonstrating that the product remains stable for 4 weeks following first opening of the container, when stored at conditions below 25°C. The drug product should be kept in the outer carton in order to protect from light.
The MAH committed to continue the stability studies until a total storage of 3 years is reached for the batches placed on long term stability testing according to the stability protocol. Results from the ongoing long term stability studies, at least up to the proposed shelf life, will be submitted as soon as available. After finalisation of the DCP, additional data were provided and the shelf life was extended from 12 to 18 months (variation NL/H/1382/001/IB/001, see table on page 8).

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.2 Non-clinical aspects

This product is a generic formulation of Xalatan eye drops, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of latanoprost released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

The excipients used in the manufacturing of Eylasol 50 µg/ml eye drops, solution are the same as the already approved innovator product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/05) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. The essential physical and chemical similarity of Eylasol 50 µg/ml with the reference product was demonstrated and therefore the exemption from biostudy can be supported. Eylasol 50 µg/ml 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.

Risk management plan
Latanoprost was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of latanoprost can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each.
In Round 1 all success criteria were fulfilled, no modification of the PL was necessary. Round 2 was therefore carried out with the same PL-version. In Round 2 also all success criteria were fulfilled.
The results of Round 1 and 2 in all three success criteria “answers/usability”, “traceability” and “comprehensibility” show that all results are 90% or higher. No problems were identified regarding comprehensibility and usefulness of information. The changes proposed to improve readability were minor lay-out changes and were approved by the member states.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Eylasol 50 µg/ml 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 biostudy.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other latanoprost containing products.

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 Eylasol 50 µg/ml, eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 6 May 2009. Eylasol 50 µg/ml was authorised in the Netherlands on 16 July 2010.

A European harmonised birth date has been allocated (5 June 1996) and subsequently the first data lock point for latanoprost is February 2012. The first PSUR will cover the period from May 2009 to February 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 5 June 2014.

The following post-approval commitments have been made during the procedure

Quality - active substance

- The MAH committed to review the water content specifications, and possibly tighten these as additional batches are manufactured.

Quality - medicinal product

- The MAH committed to continue the stability studies until a total storage of 3 years is reached for the batches placed on long term stability testing according to the stability protocol. Results from the ongoing long term stability studies, at least up to the proposed shelf-life, will be submitted as soon as available. Additional stability data have been provided, justifying an extension of the shelf life from 12 to 18 months (NL/H/1382/001/IB/001, see table below).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BAC	Benzalkoniumchloride
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Extension of shelf life of the finished product from 12 to 18 months.	NL/H/1406/ 001/IB/001	IB	14-8-2009	14-9-2009	Approval	N
A second manufacturer of the active substance latanoprost is added. The drug substance specification of the drug product manufacturer is amended to include the specification for the new API; drug product specifications remain unchanged.	NL/H/1406/ 001/II/002	II	24-7-2009	19-2-2010	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1406/ 001/IA/003	IA	27-8-2009	10-9-2009	Approval	N
Change in the name of the medicinal product in IT.	NL/H/1406/ 001/IB/004	IB	27-8-2009	28-9-2009	Approval	N
Change in the name of the medicinal product in ES.	NL/H/1406/ 001/IB/005	IB	22-3-2010	21-4-2010	Approval	N
Change in the name and/or address of a manufacturer of the finished product, including quality control sites; manufacturer responsible for batch release.	NL/H/1406/ 001/IA/006	IA	13-4-2010	13-5-2010	Approval	N
Grouped IA variations.	NL/H/1406/ 001/IA/007/ G	IA	13-7-2010	12-8-2010	Approval	N