CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Latanoprost Jelfa 0.05 mg/ml, eye drops, solution
Pharmaceutical Company Jelfa SA, Poland

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/1654/001/DC
Registration number in the Netherlands: RVG 104319

24 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:	12 July 2010
Concerned Member States:	Decentralised procedure with BG, CZ, HU, LT, LV, PL, RO, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

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 Latanoprost Jelfa 0.05 mg/ml, eye drops, solution, from Pharmaceutical Company Jelfa SA. The date of authorisation was on 12 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 hybrid application claiming essential similarity with the innovator product Xalatan 50 µg/ml eye drops, which has been registered in Sweden by Pfizer AB since 18 July 1996. 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(3) of Directive 2001/83/EC, hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

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 Latanoprost Jelfa 0.05 mg/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 hybrid 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 clear to slightly opalescent, colourless to slightly amber oil. It is practically insoluble in water and freely soluble in ethanol. Latanoprost has chiral centra resulting in four isomers. The 15R-isomer is the active isomer. The other isomers are included as impurities in the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for both suppliers of 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 is prepared in two steps. Controls of materials as well as validation of the manufacturing process have been sufficiently ensured.

Quality control of drug substance
Since latanoprost is a non-compendial drug substance, specifications were established in-house. All class 2 residual solvents used by the DMF-holders are included in the drug substance specification of the MAH. Batch analyses data of three batches have been provided. All batches complied with the specification.

Stability of drug substance
Stability data of the active substance from one supplier have been provided for 18 months (at 5 ± 3°C) for three full-scale batches. The proposed retest period of 24 months when stored at 5°C could be granted, based on the provided data.
The stability data of the active substance from the other supplier have been provided for three full-scale batches stored at 5°C/ambient humidity (6 months) and -15°C/ ambient humidity (9 to 24 months). No trends or out-of-specification values were observed. Based on these data, a retest period of 2 years stored at -15°C could be 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
Latanoprost Jelfa 0.05 mg/ml is a clear, colourless, sterile aqueous solution with a pH of 6.7±0.1 and an osmolality between 260 and 330 mOsmol/kg.

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

The solution is packed in transparent LDPE bottles with transparent LDPE dropper insert and white HDPE screw cap.

The excipients are: sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium chloride, purified water, benzalkonium chloride.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative formulation of this product is identical to the innovator and only marginal differences in the quantitative composition regarding the salts sodium chloride, sodium dihydrogen phosphate and disodium phosphate appear. No bioequivalence studies have been performed. This can be accepted as it has been demonstrated that the physicochemical parameters (pH, surface tension, viscosity and osmolality) of the originator products from the concerned member states are comparable to the drug product at issue. A sufficient justification was provided for the choice of sterilisation by filtration through a bacteria-retentive filter, followed by aseptic bottling in sterile primary packaging.
The main development studies performed are in relation to the preparation of a homogeneous latanoprost solution, suitability testing of the sterilising filter, adhesion studies, interaction studies of the packaging and the solution, and studies on suitability of the dropper inserts. An extraction and interaction study between the solution and the packaging has been performed and no interaction has been demonstrated.
The MAH demonstrated that the average drop size for the product is 30 mg; adequate dosing accuracy of the dropper insert was sufficiently demonstrated.
The pharmaceutical development of the drug product has been adequately performed.

Manufacturing process

The manufacturing process consists of the preparation of a bulk solution followed by sterile filtration and filling in the final packaging. The manufacturing process is considered to be a non-standard process. Process validation data have been presented for three full-scale batches. The predefined operation parameters were found to be suitable.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Container Closure System

Latanoprost 0.005% eye drops solution is packed in transparent LDPE bottles with a nominal capacity of 5 ml. The bottles are capped with white HDPE screw caps and transparent LDPE dropper inserts. The bottles are packed into boxes. All components of the primary packaging material are sterilized by γ-irradiation. A description of the irradiation procedure has been included.

Microbiological attributes

Latanoprost ophthalmic solution is a sterile solution and contains 0.2 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% inoculated with bacteria according to Ph.Eur. It was demonstrated that latanoprost ophthalmic solution is effectively preserved. The 0.2 mg/ml BAC is justified as the innovator uses the same concentration.

Quality control of drug product

The product specification includes test for appearance, colour, pH, relative density, osmolality, filling weight, closure integrity, delivered volume by droplet, sterility, related substances, identification of latanoprost, assay of latanoprost, identification of benzalkonium chloride and assay of benzalkonium chloride. The release and shelf-life limits only differ for the impurity latanoprost acidand 5,6-trans-Latanoprost. The shelf-life limit of the impurity 5,6-trans Latanoprost is acceptable as it is in accordance with the levels found in the originator product. The analytical methods have been sufficiently described and validated. Batch analytical data have been provided for three production-scale batches.

Stability of drug product

Stability data have been provided on 3 production-scale batches. The product was stored for a maximum of 12 months at 5°C ± 3°C and 6 months at 25°C/60%RH. The efficacy of the antimicrobial preservative has been established after 1 year of storage. Based on the available data, a shelf-life period of 12 months was granted, when stored in a refrigerator (2-8°C) and packed in a LDPE bottle with HDPE screw cap and LDPE dropper insert.

In-use stability
Two commercial-scale batches were subjected to in-use stability testing. During the study period the bottles were opened once daily and administration of the product was simulated. The in-use stability studies were conducted at the beginning of the shelf life period and towards the end of shelf life. Based on the results, an in-use period of 28 days could be granted when stored not above 25°C.

Several commitments have been made with regard to the drug product; these can be found on page 7 of this report.

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 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 Latanoprost Jelfa 0.05 mg/ml eye drops, solution with the reference product was demonstrated and therefore the exemption from biostudy can be supported. Latanoprost Jelfa 0.05 mg/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

SPC
The SPC was brought in accordance with the SPC established for procedures NL/H/1382+1404-1410/001/DC, which were positively finalised on 8 May 2009. Except RO and DE, all CMSs were involved in the procedure NL/H/1382+1404-1410/001/DC.

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 two rounds with 10 participants each. Fifteen questions were asked. Key safety messages of the PIL were covered by 10 questions. Modifications were made in between the testing rounds in order to maximise readability. The leaflet passed the success criteria. Furthermore, it was generally perceived that the PIL design/layout was easy to follow. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Latanoprost Jelfa 0.05 mg, eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid 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.

Latanoprost Jelfa 0.05 mg 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Latanoprost Jelfa 0.05 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 May 2010. Latanoprost Jelfa 0.05 mg, eye drops, solution was authorised in the Netherlands on 12 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 2010 to February 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 19 May 2015.

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

<u>Quality - medicinal product</u>

- The MAH committed to submit the results of a migration study after a storage time of 24 months.
- The MAH committed to provide further stability data upon availability to update the recommended shelf life, based on the additional results.
- The MAH committed to perform in-use stability studies intended to support the stability of the product after opening of the container for at least 28 days performed at the end-of-shelf-life on commercial-scale batches.
- The MAH committed to the results of the test on the efficacy of the preservative performed at end-of-shelf-life of a commercial scale batch.

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