CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Latanoprost NTC 50 micrograms/ml, eye drops, solution NTC Srl, Italy

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/1876/001/DC
Registration number in the Netherlands: RVG 106488

22 September 2011

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; reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.
Prescription status:	prescription only
Date of authorisation in NL:	17 August 2011
Concerned Member States:	Decentralised procedure with BG, EE, ES, IT, LT, LV, PL, RO
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 NTC 50 micrograms/ml, eye drops, solution from NTC Srl. The date of authorisation was on 17 August 2011 in the Netherlands.

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 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 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(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 NTC 50 micrograms/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., BP, USP*). Latanoprost 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. 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 consists of 3 steps. 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 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 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scale batches stored at -20°C (36 months), 2-8°C (36 months) and 25°C/60% RH (24 months). No changes are seen at all three storage conditions. Based on the data provided, the proposed retest period was granted: 36 months when protected from light and stored in a refrigerator (2-8°C).

** 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 NTC 50 micrograms/ml is a clear, colourless liquid with pH 6.2-7.1 and osmolality 240-325 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 dropper containers with LDPE under cap dropper and 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, disodiumphosphate anhydrous, sodium chloride, sodium hydroxide or hydrochloric acid for pH adjustment, water for injection.

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 and the development of the manufacturing process. The choices of the packaging and manufacturing process are justified.
The choice for the combination of aseptic filtration and aseptic processing is justified in accordance with the decision tree for sterilization choices for aqueous product, as latanoprost is heat sensitive. No overages are used in the manufacture of the drug product.
The test product contains the same active substance and in the same amount as the reference product and contain the same excipients and in the same amounts. Furthermore, the test and reference product have a similar pH, viscosity and osmolality, are the same dosage form and the drop volume is comparable. Therefore, the product at issue is considered essentially similar to the reference product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the preparation of the solution, aseptical filtering and filling into sterile bottles. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches and one full-scale batch. Process validation on two more full-scale batches will be performed post authorisation.

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

Container closure system
The primary packaging materials comply with Directive 2002/72/EC and the requirements of Ph.Eur. 3.1.3 ‘Polyolefines’ and Ph.Eur. monograph 3.1.5 ‘Polyethylene with additives for containers for parental preparations and for ophthalmic preparations’.

Microbiological attributes
The drug product is manufactured as a sterile ophthalmic solution. It contains 0.02% benzalkonium chloride as a preservative. The efficacy of antimicrobial preservation was adequately demonstrated in accordance with the requirements of the Ph.Eur. for a development batch. Furthermore, antimicrobial preservative efficacy was demonstrated during the stability studies.

Quality control of drug product
The product specification includes tests for appearance, clarity, coloration, pH, uniformity of volume, osmolality, water loss, identification, related substances, assay, benzalkoniumchloride content, sterility, particulate matter, microbial quality and efficacy of antimicrobial preservation. Except for related substances, the release and shelf-life requirements/limits are identical. Uniformity of volume is not tested at shelf-life and water loss, efficacy of antimicrobial preservation and microbial quality (after first use) are only included in the shelf-life specification. This is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches and one full scale batch, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided on two pilot-scale batches and one full-scale batch 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 LDPE bottles with LDPE dropper tip and HDPE screw cap. At both storage conditions all parameters remain with the specified limits. The

proposed shelf-life of 36 months has been granted with the applicable storage conditions 'Store in a refrigerator', 'Keep the bottle in the outer carton in order to protect from light' and 'Do not freeze'. This is acceptable in view of the forced degradation results provided.
Stability data has been provided demonstrating that the product remains stable for 4 months following first opening of the container, when stored below 25°C. The proposed shelf-life of 4 weeks after first opening for the product when stored below 25°C is justified.

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 Latanoprost NTC 50 micrograms/ml, eye drops, solution, are also used in 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 Latanoprost NTC 50 micrograms/ml with the reference product was demonstrated and therefore the exemption from biostudy can be supported. Latanoprost NTC 50 micrograms/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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Xalatan.

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 2 participants, followed by two rounds with 10 participants each. All participants were considered to be potential users and were, where possible rarely prescribed medication or admitted they had difficulty with written information relating to prescription medication.

A total number of 20 questions were asked. 17 questions specifically addressed the key safety messages of the leaflet in a randomised order and 3 were specific to the format of the package leaflet. The questions were formulated to identify all the key safety messages in the PIL and other questions were designed around those issues that would ensure a patient's comprehension and ability to act upon.

No weaknesses of the PIL were identified from the questions specifically addressing the key safety issues or from the open questions aiming to identify positive and negative impressions of the PIL (including lay-out).

Nevertheless, 5 of the 20 participants remarked that the leaflet was too long and could be shortened. However the leaflet was not shortened to avoid jeopardizing the content and validity.

8 of the 20 participants suggested more highlighting could be used in the PIL. Therefore, "prostaglandins or prostaglandin derivatives" were bolded in "Important information about some of the ingredients".

In summary, the tested package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Latanoprost NTC 50 micrograms/ml, 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 NTC 50 micrograms/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 Latanoprost NTC 50 micrograms/ml, eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 June 2011. Latanoprost NTC 50 micrograms/ml, eye drops, solution was authorised in the Netherlands on 17 August 2011.

The date for the first renewal will be: June 2016.

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

Quality - medicinal product

- The MAH committed to include three additional production-scale batches of the drug product in the stability studies under long-term conditions (36 months) and accelerated conditions (6 months).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
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