CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ofloxacine-POS 3 mg/ml, eye drops, solution
URSAPHARM Benelux B.V., the Netherlands

ofloxacin

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/2482/001/DC
Registration number in the Netherlands: RVG 110894

25 January 2013

Pharmacotherapeutic group:	ophthalmologicals, other antiinfectives
ATC code:	S01AX11
Route of administration:	ocular use
Therapeutic indication:	topical treatment of external ocular infections such as bacterial conjunctivitis and keratitis in adults and children caused by ofloxacin-sensitive organisms.
Prescription status:	prescription only
Date of authorisation in NL:	17 October 2012
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, LU and PL
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 Ofloxacine-POS 3 mg/ml, eye drops, solution, from URSAPHARM Benelux B.V. The date of authorisation was on 17 October 2012 in the Netherlands.

The product is indicated for topical treatment of external ocular infections such as bacterial conjunctivitis and keratitis in adults and children caused by ofloxacin-sensitive organisms. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

Ofloxacin is a derivative of chinolonic acid and inhibits bacterial DNA gyrase with bactericidal effect. Development of resistance to fluoroquinolones by the sensitive bacteria generally happens by mutation of the gyrA gene that codes for the A subunit of DNA gyrase. In addition, active efflux is responsible for low-level resistance that might act as a first step in resistance selection. Resistance can occur through a multistep process with subsequent mutations producing a progressively higher level of resistance in a stepwise fashion. Species of borderline susceptibility can become resistant in a single mutational step. Plasmid-mediated resistance has been found in *E. coli* and *Klebsiella* organisms.
Bacteria resistant to one fluoroquinolone show cross-resistance to other members of the quinolone-group.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Trafloxal (ofloxacin 3 mg/ml, eye drops, suspension) (NL License RVG 13510) which has been registered in the Netherlands by Bausch and Lomb Pharma N.V. since 1990. The European reference medicinal product is Floxal Augentropfen 3mg/ml, eye drops solution, registered in Germany by Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH since 1991.

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 Ofloxacine-POS 3 mg/ml, eye drops, solution 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).

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 ofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a pale yellow or bright yellow, crystalline powder which is slightly soluble in water, soluble in glacial acetic acid and slightly soluble in methanol. As the drug substance is dissolved in the course of the manufacturing process of the drug product, the polymorphic form as well as the particle size of the drug substance is not relevant. The drug substance is very sensitive to light.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the additional tests as mentioned on the CEP. 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 three batches.

Stability of drug substance
No stability data were provided as this aspect is covered by the CEP. The re-test period of the substance is 3 years.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ofloxacine-POS 3 mg/ml, eye drops, solution is a clear, pale to light yellow-green solution with pH 6.0-6.8 and osmolality of 270-330 mOsmol/kg.

The eye drops are packed in low density polyethylene (LDPE) dropper bottles with screw cap (HDPE). Each dropper bottle contains 5 ml.

The excipients are: benzalkonium chloride, sodium chloride, hydrochloric acid and sodium hydroxide solution (for pH adjustment) and water for injections.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The objective was to develop a generic version of Floxal®. The composition of the drug product was based on the composition of the reference product, and it has been adequately shown that the test en reference product are identical with respect to their physical and chemical characteristics (*e.g.* appearance, pH, osmolality, drop size, benzalkonium chloride content, impurity profile, and ofloxacin content). There are no overages of drug substance or excipients.
The development of the product has been described, the choice of the excipients justified and their functions explained. The efficacy of antimicrobial preservation has been adequately demonstrated at both the release and the proposed end of shelf-life limit. Manufacturing process development has been adequately described. The choice for aseptic filling instead of a heat treatment has also been justified.

Manufacturing process
The drug substance ofloxacin is dissolved in water for injections. The pH of the solution is adjusted. A solution of benzalkonium chloride in water for injections is added and sodium chloride is dissolved in the combined solutions. The pH is adjusted again. The bulk solution is aseptically filled into the final container.
The manufacturing process is seen as a non-standard process and has been satisfactorily described.
The manufacturing process has been adequately validated according to relevant European guidelines on two commercial scale batches. Given the experience of the drug product manufacturer with this type of product and manufacturing process on the same scale, results from 2 batches are acceptable pre-registration. Validation of the manufacturing process for a third production scale batch can be performed post registration.

Control of excipients
All excipients comply with the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification (ofloxacin and benzalkonium chloride), pH, osmolality, filling amount, loss on evaporation, assay (benzalkonium chloride and ofloxacin), related substances, absence of particles, efficacy of antimicrobial preservation, and sterility. The release requirements are acceptable. The end of shelf-life limits for the individual impurities, total impurities and for the assay (both ofloxacin and benzalkonium chloride) are wider than the release limits.
Batch analysis data have been provided on three commercial scale batches. Compliance with the proposed release requirements is demonstrated.

Stability of drug product
Stability data have been provided for three batches packed in LDPE bottles with a HDPE cap. The drug product has been stored at long-term conditions (25°C/60%RH; 18 months), intermediate conditions (30°C/65%RH; 12 months) and at accelerated conditions (40°C/75%RH; 6 months). The drug product is not stable under the influence of light and should be kept in the outer carton. During the long term and intermediate study an increase in assay of ofloxacin as well as a small increase in impurities is seen. The loss on evaporation also increases (measured at 25°C/60% RH only). Based on the stability data provided, the proposed shelf-life of 24 months, with the following additional storage conditions can be granted: ‘do not store above 25 °C. Keep the bottle in the outer carton in order to protect from light’. The in-use stability has been adequately demonstrated for the claimed shelf-life after opening of 4 weeks.

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 Floxal Augentropfen 3mg/ml, eye drops solution, which is available on the European market. 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. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

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 ofloxacin 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. However, a short environmental risk assessment was provided.
$PEC_{surface\ water}$ for ofloxacin value is below the action limit of 0.01 µg/L and ofloxacin is not a PBT (persistent, bioaccumulative and toxic), nor vPvB (very persistent and very bioaccumulative) substance as log K_{ow} does not exceed 4.5.

II.3 Clinical aspects

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

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For oral solutions no bioequivalence studies are necessary, however excipients which may affect absorption etc. should be taken into account. This is also applicable for this aqueous ofloxacin eye drops solution. 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. This formulation is qualitatively and quantitatively identical to the reference medicinal product. A biowaiver is acceptable.
Ofloxacine-POS 3 mg/ml, eye drops, solution 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
Ofloxacin was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ofloxacin 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 Floxal Augentropfen 3mg/ml, eye drops solution.

Readability test
Readability testing was performed on the package leaflet. A pilot round (3 respondents) was performed, which did not lead to changes of the package leaflet, after which a readability user test with 20 test subjects was started.
A questionnaire of 15 questions specific to the medicinal product was drawn up, sufficiently addressing the key safety messages. In addition, 4 questions were asked about the layout and design, and 2 open questions on what persons liked about the PL and how the PL could be improved.
Overall, the interviews showed that the information of the PL was found and well understood. The test result meets the corresponding success criteria of the “Guideline on the readability of the labelling and

package leaflet of medicinal products for human use", stating that a satisfactory test outcome is when the information requested within the package leaflet can be found by 90% of test participants, of whom 90% can show that they understand it.
The test subjects were satisfied with the readability of the text, the clarity of the text, the graphical layout, and the font style and size. Suggestions on the PL have been given by the participants, but these have not been discussed in the report.
Overall, the results of the test indicate that the package leaflet is easy to understand and written in a comprehensible manner, meeting the requirements of European Directive 2001/83/EC as amended by Directive 2004/27/EC.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ofloxacine-POS 3 mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Floxal Augentropfen 3mg/ml, eye drops solution. Floxal is a well-known medicinal product with an established favourable efficacy and safety profile.

A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.
Ofloxacine-POS 3 mg/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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ofloxacin 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 Ofloxacine-POS 3 mg/ml, eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 September 2012. Ofloxacine-POS 3 mg/ml, eye drops, solution was authorised in the Netherlands on 17 October 2012.

The date for the first renewal will be: 11 September 2017.

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

Quality - medicinal product

- The MAH committed that validation of a third batch on commercial scale will be performed post approval. The data should be submitted upon request or if unexpected results/events occur.
- The MAH committed to continue the stability tests already started with three production scale batches throughout the shelf-life of three years.
- The MAH committed to perform at least one further in-use test towards the end of shelf life.

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