CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ofloxacine Eberth 3 mg/ml eye drops, solution
Dr. Friedrich Eberth Arzneimittel GmbH, Germany

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/2392/001/DC
Registration number in the Netherlands: RVG 109911

22 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:	26 November 2012
Concerned Member States:	Decentralised procedure with AT, DE, ES 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 Eberth 3 mg/ml eye drops, solution, from Dr. Friedrich Eberth Arzneimittel GmbH. The date of authorisation was on 26 November 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.

The derivative of chinolonic acid, ofloxacin, is a gyrase inhibitor of the fluoroquinolone sub-group 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, solution) (NL License RVG 13510) which has been registered in the Netherlands by Bausch & Lomb Pharma 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 Eberth 3 mg/ml eye drops, solution is a product for ocular use (eye drops) intended to act without systemic absorption, with qualitatively 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 this product 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 ofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is used as a racemate. It is a pale yellow or bright yellow, crystalline powder, which is slightly soluble in water. 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 accordance with the Ph.Eur. and the CEP and contains additional requirements for microbial contamination. The specification is acceptable.
Batch analytical data demonstrating compliance with the drug substance specification were provided for two commercial-scale 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
Ofloxacin Eberth 3 mg/ml eye drops, solution is a clear, slightly greenish yellow solution with pH 6.5 to 7.5 and osmolality of 260 to 330 mOsmol/kg.

The eye drops are packed in 5 mL LDPE dropper containers with PE tamper-proof screw cap.

The excipients are: benzalkonium chloride, sodium chloride, hydrochloric acid and sodium hydroxide-solution (for pH-adjustment), water for injections. The excipients are usual for this type of dosage form.

Pharmaceutical development
Formulation development was sufficiently described. The choice of excipients is justified and their functions explained. The quantitative composition of the drug product in terms of the active ingredient ofloxacin and the qualitative composition of the drug product in terms of excipients is identical with the reference medicinal product Floxal eye drops, solution, a formulation containing 3 mg/mL ofloxacin. The

eye drops are preserved with 0.025 mg/ml (0.0025% w/v) of benzalkonium chloride. This is lower than described in the Handbook of Pharmaceutical Excipients according to which benzalkonium chloride is used in concentrations of 0.01 to 0.02%(w/v) in ophthalmic formulations, but it is in line with the reference product. Due to the local action of the drug product, no bioequivalence study was performed. Instead, the MAH compared the generic and the reference product Floxal Augentropfen 3 mg/ml, eye drops, solution with regard to physicochemical parameters (pH, relative density, osmolality, ofloxacin content, benzalkonium chloride content, sodium chloride content and related substances) and dose per drop. Comparison of the generic and the reference product did not include the parameter viscosity, presumably as no viscosity-increasing agent is included in the formulation. This is acceptable. The generic and reference products are considered to be comparable from a chemical-pharmaceutical point of view. There are no overages of drug substance or excipients. In order to guarantee the nominal declared amount in the dropper bottles, an overfill of about 0.35 mL per container is applied.
The drug product can not be terminally sterilized due to the heat-labile container closure system. An acceptable justification was provided for the choice of the container closure system. The drug product is filtered through a sterilizing grade filter and aseptically filled. The empty container closure system is sterilized by gamma sterilization.
Efficacy of antimicrobial preservation was shown at a level of 80% of the target benzalkonium chloride concentration, which offers a sufficient margin of safety towards the lower release and shelf life limit.

Manufacturing process
The manufacturing process involves dissolution of the drug substance and excipients in water for injections, sterilisation by filtration and aseptic filling. The manufacturing process was sufficiently described. Due to the aseptic processing step, the manufacturing process is considered to be non standard, requiring process validation on three consecutive production-scale batches. The manufacturing process was adequately validated with three full-scale batches.

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 (clarity and opalescence, colour), identity of ofloxacin and benzalkonium chloride, relative density, pH, osmolality, assay of ofloxacin and benzalkonium chloride, purity, sterility, particulate contamination (sub-visible particles), extractable volume, evaporative loss, and efficacy of antimicrobial preservation. The release and shelf life specifications differ with regard to the limits for related substances. The proposed drug product specification is acceptable.
The analytical methods were adequately described and validated.
Batch analytical data from the proposed production site were provided on one batch of the largest proposed commercial batch size and on five batches of half of the size. All batches complied with the release specification.

Stability of drug product
Stability data on the product was provided on six batches (one batch of the largest proposed commercial batch size and on five batches of half this batch size) stored at 25°C/60% RH (three batches for 24 months and three batches for 12 months), 30°C/65% (12 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. Stability studies were not conducted under conditions of low relative humidity, but the evaporative loss at conditions of low relative humidity was calculated by the ratios specified in the *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products*.
A considerable difference was observed in impurity levels in the three older and the three newer stability batches. This was explained with the fact that the older batches were packed in transparent and the newer batches in white LDPE bottles. Based on the provided stability results, a shelf life of 24 months can be approved. Storage conditions are “Do not store above 25°C” (based on trends with regard to related substances and evaporative loss), “Do not refrigerate or freeze” (as a negative effect of storing the drug product in the refrigerator can not be ruled out due to the low solubility of the drug substance), and “Keep bottle in outer carton in order to protect from light” (based on photostability data). A simulated consumer

use study has confirmed the in-use stability of the drug product over a period of 4 weeks, demonstrating adequate efficacy of antimicrobial preservation.

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.

Substance (INN/Invented Name): Ofloxacin			
CAS-number (if available): 82419-36-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.48	not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.48	not B
	BCF	not assessed	
Persistence	DT50 or ready biodegradability	not assessed	
Toxicity	NOEC or CMR	not assessed	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0043	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)	not assessed		

$PEC_{surface\ water}$ 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 drop

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 identical to the reference medicinal product. A biowaiver is acceptable.
Ofloxacine Eberth 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 based on that accepted for the reference product Floxal Augentropfen 3mg/ml, eye drops solution and has been amended in accordance with current knowledge.

Readability test
Readability testing was performed for the German package leaflet of a product which has the same qualitative and quantitative composition as Ofloxacine Eberth Unit Dose 3 mg/ml eye drops, solution. Both medicinal products are manufactured by the same manufacturer.
Both products are ophthalmic preparations proposed for the same indications and containing the same active substance in the same strength. Thus, the product information for the two products is comparable.

Both PLs are similar in layout and content. The successful user test is also applicable for Ofloxacine Eberth.The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ofloxacine Eberth 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 Eberth 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 based on 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 Eberth 3 mg/ml eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 31 August 2012. Ofloxacine Eberth 3 mg/ml eye drops, solution is authorised in the Netherlands on 26 November 2012.

The date for the first renewal will be: 31 August 2017.

There were no post-approval commitments made during the procedure.

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