CBG MEB

Public Assessment Report

Scientific discussion

Ofloxacine Regiomedica 3 mg/ml, eye drops, solution, single dose container

(ofloxacin)

NL/H/2858/001/DC

Date: 17 November 2014

This module reflects the scientific discussion for the approval of Ofloxacine Regiomedica 3 mg/ml, eye drops, solution, single dose container. The procedure was finalised on 3 July 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ofloxacine Regiomedica 3 mg/ml, eye drops, solution, single dose container, from Regiomedica GmbH.

The product is indicated for the topical treatment of external ocular infections (such as 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 SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Trafloxal 3 mg/ml eye drops (NL License RVG 13510) which has been registered in the Netherlands by Bausch and Lomb Pharma since 24 July 1990.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. This is a hybrid application as bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Ofloxacine Regiomedica 3 mg/ml is a clear, pale light yellow solution, free from visible particles with pH 6.0–6.8 and Osmolality of 270 – 350 mosmol/kg. Each ml contains 3 mg ofloxacin in a preservative free formulation for administration by instillation in the conjunctival sac.

The solution is packed in 0.5 ml transparent LDPE single-dose containers in PET aluminium/PE sachets containing 5 single dose containers each.

The excipients are: sodium chloride, sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), purified water.

II.2 Drug Substance

The active substance is ofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a pale yellow or bright yellow, crystalline powder, which is slightly soluble in water, soluble in glacial acetic acid, slightly soluble or soluble in methylene chloride and slightly soluble in methanol. Ofloxacin is a racemate.

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
In addition to the requirements for ofloxacin described in the current monograph of the Ph.Eur. and the current CEP the following microbiological tests are performed: total aerobic microbial count and total

combined yeasts and moulds. Batch analysis data on three batches is provided. Sufficient information on reference standards or materials was provided.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH has provided the results of a comparative *in vitro* study between three batches of the test product versus three batches of the reference product. According to the Guideline on Investigation of Bioequivalence, a waiver of clinical studies for locally acting locally applied drug products may be acceptable in the case of solutions, *e.g.* eye drops. Here the relevant requirements for a biowaiver have been fulfilled: It concerns the same type of (aqueous) solution, the same concentration of the same active substance, the same method and means of administration as well as the same quantitative composition. Pharmaceutical equivalence was sufficiently demonstrated for the relevant pharmaceutical properties by the results of the *in vitro* comparison, which showed that test and reference product have a similar droplet size, pH, relative density, osmolality, viscosity, surface tension and impurity profile. Therefore the biowaiver can be accepted.

The development studies performed included stability studies at low temperatures (from -20°C to 5-8°C) up to 28 days, showing no effect of temperature on solubility of ofloxacin in aqueous solution.
The excipients used in the product are well known. The choices of the packaging and manufacturing process are justified. The MAH has explained why terminal sterilisation in the final container was not pursued. There is no incompatibility of the active substance with any of the excipients or with the packaging material.

Manufacturing process
The manufacturing process is a non-aseptic process of weighing and mixing. Subsequent filtration, filling and sealing of the containers are aseptic processes. Once the unit-dose container is moulded in the machine, the solution is filled. The manufacturing process includes in its final steps a sterilizing filtration. This sterilisation method has been justified. Process validation data on the product have been presented for 3 commercial-scale batches, demonstrating compliance with the requirements.

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

Microbiological attributes
Microbiological control of the solution before filtration meets the requirements described in Ph.Eur. sections 2.6.12 and 2.6.13. Once the solution is filtrated, the solution meets the requirement for sterile products.

Quality control of drug product
The product specification includes tests for identification, clarity, degree of colouration, pH, relative density, osmolality, extractable volume, uniformity of dosage unit, integrity of the single-dose container and the sachet, assay, related substances and sterility. The release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. The method for related substances is stability indicating. Batch analytical data from the proposed production sites have been provided on three batches per presentation. The batch sizes correspond with commercial batch size and comply with the proposed specifications.

Stability of drug product
Stability data have been provided for three production scale batches. These were stored at 25°C/40% RH for 36 months and 40°C/NMT25% RH up to 6 months. The conditions used in the stability studies are in accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in semi-permeable containers. All batches comply with the proposed set of specifications, at both temperatures tested. During long term stability studies a slight decrease in extractable volume occurred and an increase in the degradation product with RRT 0.8 over time,

especially after the 24 month time point. However, all tests remain within specifications up to 36 month. The results of the accelerated studies show a slight increase in osmolality, a slight decrease in extractable volume and a slight increase in content of ofloxacin. No increase in degradation products is seen in this 6 month period. All values remain within specifications.
In-use stability data (temperature: 25ºC/40% RH) were collected for all three development batches at release and for one batch at the end of shelf-life. For batches at the start of their shelf-life, in the 28 days of the study, a decrease in extractable volume and a slight increase in content of ofloxacin was seen. For the batch at the end of its shelf-life a slight increase in degradation products was seen, however all values remained within the specifications. Data on photostability of the drug product were included and it was shown that the drug product should be protected from light. The proposed shelf-life of 36 months is justified. The proposed storage condition 'Store in the original package (sachet) in order to protect from light' is acceptable.

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.4 Discussion on chemical, pharmaceutical and biological aspects

CMD(h) referral
Ground for referral
The procedure was referred to the CMD(h) due to a different insight regarding the GMP status of the finished product manufacturer. As the GMP certificate for this manufacturer was more than 3 years old, the Dutch Inspectorate (IGZ) provided the company with a GMP certificate based on a distant assessment in order to cover for the period until the next GMP site inspection.
The CMS involved in this procedure did not accept this approach, as from a formal standpoint of view, a distant assessment of a sterile manufacturer is not allowed.
The CMS was of the opinion that a valid GMP certificate should be available before the procedure can be finalised positively.

Referral outcome
An on-site (re-)inspection of the finished product manufacturer was performed in March 2014. After the discussion in CMD(h) meeting, it was confirmed by the inspectors that the outcome of the inspection is considered positive and that a GMP certificate for this manufacturing site will be issued.
Agreement in the CMD(h) was reached by day 60 and the procedure was finalised positively.

Based on the submitted dossier, the member states consider that Ofloxacine Regiomedica 3 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:
- Every year, if a new batch of the drug substance ofloxacin is manufactured, samples of this new batch will be introduced to on-going stability studies on long term storage condition 25 ± 2°C/60 ± 5% RH

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ofloxacine Regiomedica is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Trafloxal 3 mg/ml eye drops which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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.

IV.2 Pharmacokinetics

Biowaiver
No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative attributes of the 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. Since the qualitative and quantitative composition of the product is similar to that of the reference product Trafloxal 0.3 mg/ml eye drops, and the pharmaceutical properties (*i.e*. osmolarity, pH, relative density) are comparable to that of the reference product as well, a biowaiver can be granted. Ofloxacine Regiomedica 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.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ofloxacine Regiomedica.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity
Important potential risks	Potential reduction of effectiveness of ofloxacin when administered with ophthalmic products containing heavy metals (for example zinc)
Missing information	Use in paediatric patients (especially in infants below 1 year of age)
	Use during pregnancy and lactation

The safety profile of ofloxacin can be considered to be well established and no product specific pharmacovigilance issues have been identified. Therefore the member states consider that routine pharmacovigilance measures are sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Trafloxal 0.3 mg/ml eye drops. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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. A questionnaire of 14 questions specific to the medicinal product was drawn up, sufficiently addressing the key safety messages. In addition, 5 questions were asked about how the participants evaluated the test and PL (*e.g.* was it difficult to read, what do they think is important information etc.).
Overall, the interviews showed that the information of the PL was found and well understood. The test subjects were in general satisfied with the readability of the text, all of them found easily the most important information in the leaflet. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ofloxacine Regiomedica 3 mg/ml, eye drops, solution, single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Trafloxal 0.3 mg/ml eye drops. Trafloxal is a well-known medicinal product with an established favourable efficacy and safety profile

As Ofloxacine Regiomedica 0.3 mg/ml is a product for ocular use (eye drops) intended to act without systemic absorption, with a comparable composition to the reference product, it is exempted for biostudy.

In the Board meeting of 5 June 2014, the GMP status of the manufacturer of the finished product was discussed. Based on the positive new inspection report, the Board considered that GMP compliance is warranted.

Agreement between member states was reached during a CMD(h) referral. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ofloxacine Regiomedica with the reference product, and have therefore granted a marketing authorisation. The CMD(h) referral procedure was finalised with a positive outcome on 3 July 2014.

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