COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levofloxacine Rafarm preservative free 5 mg/ml eye drops, solution

(levofloxacin hemihydrate)

NL/H/4549/001/DC

Date: 6 January 2020

This module reflects the scientific discussion for the approval of Levofloxacine Rafarm preservative free 5 mg/ml eye drops, solution. The procedure was finalised on 4 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levofloxacine Rafarm preservative free 5 mg/ml eye drops, solution from Rafarm SA.

The product is indicated for the topical treatment of bacterial external ocular infections in patients ≥1 year of age caused by levofloxacin susceptible microorganisms (see also sections 4.4 and 5.1 of the approved SmPC).

The product is indicated in adults, children aged ≥1 year to 12 years and adolescents aged 12 to 18 years.
Considerations 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 similarity with the innovator product Oftaquix 5 mg/ml eye drops, solution, which has been registered via the mutual recognition procedure (UK/H/0464/001/MR) by Santen Oy since 2002. Due to the Brexit, the RMS of Oftaquix has been switched to Finland (FI/H/0989/001).

The concerned member states (CMS) involved in this procedure were Cyprus, Greece, Italy, Poland and Portugal. The reference product Oftaquix is registered in Italy and Portugal. Oftaquix is used as a European Reference Product in the RMS and CMSs Cyprus, Greece and Poland.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Levofloxacine Rafarm is a clear with a light yellow colour solution, with no visible particles, with pH 6.0-7.0 and osmolality of 260 to 340 mOsmol/kg. One ml of eye drops, solution, contains 5.12 mg of levofloxacin hemihydrate, equivalent to 5 mg of levofloxacin.

Each drop contains approximately 0.2 mg of levofloxacin hemihydrate, equivalent to 0.195 mg of levofloxacin.

The solution is packed in white opaque LDPE bottle and white Novelia nozzle (HDPE and silicone) and sealed with a white HDPE cap.

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

II.2 Drug Substance

The active substance is levofloxacin hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Also a United States Pharmacopoeia (USP) monograph for levofloxacin hemihydrate is available. The active substance is freely soluble in acetic acid, slightly soluble in water, methanol, and ethanol. Levofloxacin hemihydrate is the S-isomer of ofloxacin. The active substance exhibits pseudo-polymorphism (hemihydrate and monohydrate).

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
Levofloxacin hemihydrate is synthesized in four steps. The first step is outsourced, and the second step may be outsourced or performed in-house. In the final step methanol is used as a solvent. The starting materials are acceptable. The active substance is adequately characterized.

Quality control of drug substance
The drug substance specification of the MAH has been established in line with the specifications of the ASMF-holder. 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 on three batches. Based on these data the proposed retest period of 24 months with storage condition "Store in well closed, air tight and light resistant containers at controlled room temperature" is acceptable.

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 main development studies concerned the characterization of

the reference product and comparative characteristics studies. The comparative studies included parameters appearance, assay, coloration, related substances, specific gravity, viscosity, surface tension, pH, osmolality and drop size. The same excipients as in the reference product were selected. Both drug products can be regarded as therapeutically equivalent from a chemical-pharmaceutical point of view and therefore the criteria for a biowaiver are met. The test and reference product have the same quantitative composition, also the same dose is delivered.

The reference product is presented in a single-dose container of 0.3 mL for ophthalmic use. The pharmaceutical development of Levofloxacin Rafarm 5 mg/ml was carried out in order to obtain a multi-dose version of the reference product. The container closure system for Levofloxacin Rafarm 5 mg/ml, eye drops solution comprises a novel packaging and delivery system (Novelia) containing the formulation as a bulk sterile solution with a mechanism to dispense individual drops from the bulk. The design includes a one-way valve and a silicone plug which protect the product from microbial contamination enabling the product to be formulated without preservatives. Silver ions are embedded into the cap and the top in order to maintain sterility in any product remaining on the surface of device. The suitability of the container closure system is justified as additional data have been provided demonstrating sterility assurance during 28 days of use. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of preparing the bulk solution, sterile filtration through a bacterial retentive filter followed by aseptic filling into the LDPE bottles. Process validation data on the product has been presented for three smallest production-scale batches. The manufacturing process is described in sufficient detail.

Control of excipients

The excipients comply with pharmacopoeial requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, coloration, pH, osmolality, identification, assay, related substances, particulate matter, extractable volume, container closure integrity, water loss and sterility. The release and shelf-life specifications differ with regard to the acceptance criteria for related substances and water loss. The drug product specification is acceptable. Batch analytical data have been provided on three industrial-scale batches. The batch analytical data comply with the specification.

Stability of drug product

Stability data on the product has been provided for three commercial-scale batches stored at 25°C/60% RH (24 months), 30±2°C/65±5%RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. An increase in water loss is observed at intermediate conditions. Based on the provided stability data, the proposed shelf life of 36 months has been granted. Photostability results indicate

that the drug product is susceptible to photo-degradation and that a sole opaque bottle is not adequate. As such, the product should be stored in the outer packaging in order to protect from light. The storage condition "Store in the original package, as the product is sensitive to light" is justified.
The in-use stability of 28 days can be granted since in-use stability testing has been performed on two batches.

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

Based on the submitted dossier, the member states consider that Levofloxacine Rafarm preservative free 5 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitment was made:
- The MAH committed to perform a risk assessment for the potential presence of nitrosamines in the finished product, considering risk assessment reports of the API supplier and other materials suppliers as well.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levofloxacine Rafarm preservative free 5 mg/ml 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 Oftaquix, 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

Levofloxacin 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 clinical and bioequivalence studies have been conducted to support the application. Essential similarity with the reference product is based on the comparative quality attributes of the product. The proposed product has the same quantitative composition and the same type of solution as that of the reference product. Hence, the absence of a bioequivalence study is agreed in line with the bioequivalence guideline and the provided data is regarded sufficient to support the application. Levofloxacine Rafarm preservative free 5 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.

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 Levofloxacine Rafarm.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Anaphylaxis - Laryngeal oedema - Eye disorder including eye irritation, decreased vision, chemosis, conjunctival papillary reaction, ocular pain, conjunctival injection and photophobia
Important potential risks	- Use in pregnant women - Use in breastfeeding women
Missing information	- Use in children under 1 year of age - Specific drug interactions

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Oftaquix. No new clinical studies were conducted. The MAH demonstrated essential similarity with the reference product based on comparative quality attributes. Risk management is adequately addressed. This hybrid 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. It included an appropriate testing panel of 11 male and 9 female subjects of various age and education. The questions covered various sections of the PL and addressed key messages. The data shows the participants were able to correctly locate the answer the questions in 95% of the time and to correctly answer the questions 95% of the time. The participants were given ample time to answer each question. The interviewer performed the testing in an appropriate fashion. No issues have been identified.
The results show that the PL 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

Levofloxacine Rafarm preservative free 5 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Oftaquix eye drops, solution. Oftaquix is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes. A biowaiver has been granted.

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 Levofloxacine Rafarm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 December 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse