IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Levofloxacin 500 mg Film-coated Tablets
Levofloxacin
PA0688/052/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Levofloxacin 500 mg Film-coated Tablets,from Chanelle Medical on 3rd July 2020 for:
Levofloxacin is indicated in adults for the treatment of the following infections.
•Acute pyelonephritis and complicated urinary tract infections
•Chronic bacterial prostatitis
•Inhalation Anthrax: postexposure prophylaxis and curative treatment

For the below-mentioned infections Levofloxacin Tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
•Acute bacterial sinusitis
•Acute exacerbations of chronic obstructive pulmonary disease including bronchitis
•Community-acquired pneumonia
•Complicated skin and soft tissue infections
•Uncomplicated cystitis

This national application has been submitted under Article 10(1) of Directive2001/83/EC referred to as a generic application. Levofloxacin is an antibiotic which is a prescription only product.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Levofloxacin 500 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Levofloxacin as levofloxacin hemihydrate
Pharmacotherapeutic classification (ATC code)	J01MA12
Pharmaceutical form and strength(s)	500 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0688/052/001
Marketing Authorisation Holder	Chanelle Medical

II. QUALITY ASPECTS

II.1. Introduction

This application is for Levofloxacin 500 mg Film-coated Tablets.

II.2 Drug substance

The active substance is levofloxacin (as hemihydrate), an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet contains 500 mg of levofloxacin as levofloxacin hemihydrate.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets,and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. /EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Levofloxacin 500 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Tavanic (Sanofi Aventis) on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

N/A

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Tavanic 500mg film coated tablet marketed by Sanofi Aventis.

For this generic application,the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Levofloxacin 500mg film coated tablet is compared with the pharmacokinetic profile of the reference product Tavanic 500mg film coated table Aventis Pharma Deutschland GmBH.

A single-dose, randomised,two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Levofloxacin 500mg film coated tablet from Chanelle Medical, was compared to the reference product Tavanic 500mg film coated tablet from Aventis Pharma Deutschland GmBH. Based on the pharmacokinetic parameters of active substance, the reference tablet Tavanic 500mg film coated tablet marketed by Aventis Pharma Deutschland GmBH and test tablet Levofloxacin tablet 500mg were bioequivalent with extent to the rate and extent of absorption. However, because data was not available to satisfactorily resolve issues raised with regard to the bioanalytical method it could not be concluded that the bioequivalence requirements outlined in the relevant CHMP Note for Guidance were fulfilled. The bioanalytical method was validated and the bioequivalence study completed prior to the coming into effect of the EMA Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr, 2**.
Therefore, the applicant chose to request a biowaiver on the basis that levofloxacin is a BCS category 1 drug (it is highly soluble and demonstrates complete absorption) and that it did not contain any excipients that affect the rate or extent of absorption. To support this, the applicant provided a solubility study for the active substance, a comparative in-vitro dissolution study between Levofloxacin 500mg tablet and Tavanic 500mg, and a qualitative comparison of the excipients.
It was concluded that the conditions for a biowaiver were met: Levofloxacin is a BCS Class 1 drug. Levofloxacin 500mg tablet contains the same salt as Tavanic. It was highly soluble, and demonstrated at least 90% dissolution within 15 minutes in three different pH media and the dissolution profile was similar to the reference product Tavanic. The excipients are qualitatively similar and are unlikely to influence solubility or absorption. Therefore it can be concluded that Levofloxacin 500mg tablet is bioequivalent to Tavanic 500mg film coated tablet.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Tavanic marketed by MAH.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption

Levofoloxacin administered orally is rapidly and almost completely absorbed, with peak plasma concentrations obtained within 1-2 hours. The absolute bioavailability is 99 - 100 %. Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues. Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blisterfluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebro-spinal fluid.

Biotransformation

Levofloxacin is metabolised to a very small extent to the following metabolites desmethyl-levofloxacin and levofloxacin N-oxide, which make up < 5% of the dose and are excreted in urine.

Elimination

Following oral and IV administration, levofloxacin is eliminated slowly from plasma (t1/2: 6 – 8hours). Excretion is mainly renal (> 85% of the administered dose).

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Special populations

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased.

IV.3 Pharmacodynamics

Fluoroquinolone antibiotics target bacterial DNA gyrase and topoisomerase IV.

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNAgyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa)* and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

IV.4 Clinical Efficacy

N/A

IV.5 Clinical Safety

The safety of levofloxacin is well characterised.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

The submitted RMP is considered acceptable (Version 1.0 Date of final sign off: 24/10/2016).

The Summary of Safety Concerns is as follows:
Important identified risks:

- Tendonitis and tendon rupture
- Superinfection –including Clostridium Difficile associated disease (CDAD) and antibiotic association colitis
- Seizures in predisposed patients
- Joint toxicity in children and growing adolescents
- Haemolytic reactions in patients with G-6-phosphate dehydrogenase deficiency
- Hypersensitivity reactions / anaphylactic reactions
- Severe cutaneous adverse reactions including severe bullous reactions
- Dysglycaemia
- Photosensitisation
- Psychotic reactions
- QT interval prolongation
- Peripheral neuropathy
- Hepatotoxicity including hepatic necrosis
- Exacerbation of Myasthenia Gravis
- Vision disorders
- Nephrotoxicity (renal failure)
- Interaction with ciclosporin
- Interaction with Vitamin K antagonistsImportant potential risks:

- Interaction with probenecid and cimetidine
- Retinal degradation and retinal detachmentMissing information:

- Use during pregnancy
- Use during breastfeeding

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit risk profile of the product and detect any safety concerns.

PSUR frequency
For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.6 Discussion on the clinical aspects

Because data was not available to satisfactorily resolve the issues raised with regard to the bioanalytical method the applicant sought approval based on meeting the conditions for a biowaiver.
It was concluded that the conditions for a biowaiver were met: Levofloxacin is a BCS Class 1 drug. Levofloxacin tablet 500mg contains the same salt as Tavanic. It was highly soluble, and demonstrated at least 90% dissolution within 15 minutes in three different pH media and the dissolution profile was similar to the reference product Tavanic. The excipients are qualitatively similar and are unlikely to influence solubility or absorption. Therefore, it can be concluded that Levofloxacin 500mg film coated tablet is bioequivalent to Tavanic 500mg film coated tablet.

V. OVERALL CONCLUSIONS

Because data was not available to satisfactorily resolve issues raised with regard to the bioanalytical method, the applicant sought approval based on meeting the conditions for a biowaiver.
It was concluded that the conditions for a biowaiver were met: Levofloxacin is a BCS Class 1 drug. Levofloxacin 500mg film coated tablet contains the same salt as Tavanic. It was highly soluble, and demonstrated at least 90% dissolution within 15 minutes in three different pH media and the dissolution profile was similar to the reference product Tavanic. The excipients are qualitatively similar and are unlikely to influence solubility or absorption. Therefore, it can be concluded that Levofloxacin 500mg film coated tablet is bioequivalent to Tavanic 500mg film coated tablet.
Levofloxacin 500mg film coated tablet (Levofloxacin hemihydrate) is a generic form of Tavanic. Tavanic is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Levofloxacin 500mg film coated tablet demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES