CBG MEB

Public Assessment Report

Scientific discussion

Levofloxacine Beximco 250 mg and 500 mg, film-coated tablets

(levofloxacin hemihydrate)

NL/H/3238/001-002/DC

Date: 11 July 2016

This module reflects the scientific discussion for the approval of Levofloxacin Beximco 250 mg and 500 mg, film-coated tablets. The procedure was finalised on 26 October 2015. 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
BP	British 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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levofloxacine Beximco 250 mg and 500 mg, film-coated tablets, from Beximco Pharma UK Ltd.

The product is indicated for in adults for the treatment of the following infections:

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections

For the above-mentioned infections Levofloxacine Beximco should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- Pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis
- Uncomplicated cystitis
- Inhalation Anthrax: post exposure prophylaxis and curative treatment

Levofloxacine Beximco may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.

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 generic application claiming essential similarity with the innovator product Tavanic 250 mg and 500 mg film-coated tablets (NL License RVG 21811-21812), which has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 9 December 1997 through mutual recognition procedure UK/H/0203/001-2.

The concerned member states (CMS) involved in this procedure were Bulgaria, Malta and Poland.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product is a film-coated tablet in the strengths of 250 mg and 500 mg levofloxacin. Each tablet contains 250 mg or 500 mg levofloxacin as levofloxacin hemihydrate.

Both tablet strengths are pink, capsule shaped, biconvex with a break line and debossed with two letters on either side of the break line on one face. The 250 mg film-coated tablets are debossed with ‘L’ and ‘F’, while the 500 mg film-coated tablets are debossed with the letters ‘L’ and ‘V’.

The film-coated tablets are packed in clear transparent PVC-AL blisters

The excipients are:
Tablet core
- Crospovidone Type B, E1202
- Povidone K- 30, E1201
- Cellulose, Microcrystalline, E460

- Silica, colloidal anhydrous, E551
- Magnesium stearate, E572

Film-coat
- Hypromellose, E464
- Talc, E553b
- Titanium dioxide, E171
- Macrogol 400, E1521
- Ferric oxide red, E172
- Ferric oxide yellow, E172

The two tablet strengths are dose proportional and can be divided into equal doses.

II.2 Drug Substance

The active substance is levofloxacin hemihydrate, an active substance not described in the European or British Pharmacopoeia (Ph.Eur.; BP). A monograph is available in the United States Pharmacopoeia (USP) and a draft monograph is published in Pharmeuropa. The drug substance is a light yellowish-white to yellow-white crystal or crystalline powder.
According to literature levofloxacin exhibits polymorphism and different hydrates such as anhydrous, hemi hydrate and monohydrate forms. It has been shown that no other polymorphs than the hemihydrate for levofloxacin are manufactured. Levofloxacin hemihydrate is the (-)-S-isomer of ofloxacin. The molecule exists as a zwitterion at the pH conditions in the small intestine.

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
The manufacturing of levofloxacin hemihydrate consists of three steps. The ASMF-holder provided sufficient details about the synthesis route, including a specification for limiting the R-enantiomer.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Six batches have been tested on stability including three batches of a larger size (24-60 months at 25°C/60% RH, 6 months at 40°C/75% RH). Storage under these long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable during the storage period of 60 months. The proposed re-test period of 60 months is considered acceptable when the product is stored in an air-tight container, protected from light at controlled room temperature.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The innovator product was characterized and the development was based on these results. Relevant optimization studies on the excipients and manufacturing process were performed. Both strengths of the generic product have score lines, and the tablets have been shown to fulfil the requirements for subdivision of tablets.

A bioequivalence study has been performed with the 500 mg product strength versus its respective reference product strengths. The 500 mg batches used in the bioequivalence study were

manufactured according to the finalized composition and manufacturing process. Sufficient comparative dissolution data between the test and reference product have been provided.

For the 250 mg tablets a biowaiver was justified. The biowaiver is based on the bioequivalence study with the 500 mg product. Both batches comply with the general biowaiver criteria and it has been sufficiently demonstrated that dissolution of the 250 mg batch is similar to that of the 500 mg bioequivalence study test batch under the relevant dissolution conditions (0.1N HCl, pH 4.5 and pH 6.8). The 250 mg and 500 mg film-coated tablets are fully dose proportional and are manufactured using the same manufacturing process.

Manufacturing process
The manufacturing process consists of several steps, including dispensing, sifting, dry mixing, granulation, milling, sifting, blending and lubrication. Subsequently the tablets are compression and film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
All excipients meet the requirements of the corresponding Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for dispensing, sifting, dry mixing, granulation and wet mixing, wet milling/screening, milling, sifting (extra granular excipients), blending and lubrication, compression, and film-coating. The proposed specification is the same with the exception of limits for related substances, dissolution and disintegration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of both strengths from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches of each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Results remained within limits and no specific trends or patterns are noted. The product remains stable for 24 months under long term conditions and 6 months accelerated conditions. Based on these results, the proposed shelf-life of 24 months is considered acceptable. A storage condition is not considered necessary. The product is considered to be photostable.

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 Beximco has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments have been made:

- The MAH committed to re-evaluate the end of shelf-life limit for dissolution (tested at the 30-min as well as the 45-min time point) as more stability data become available, and amend the specification if necessary.
- The MAH commits to conduct process validation for another proposed batch size.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levofloxacine Beximco 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 generic formulation of Tavanic film-coated tablets which are 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.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Levofloxacine Beximco 500 mg film-coated tablets (Beximco Pharma UK Ltd, UK) is compared with the pharmacokinetic profile of the reference product Tavanic 500 mg film-coated tablets (Sanofi-Aventis, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was granted for the 250 mg product, based on the bioequivalence study conducted on the 500 mg strength. Hence the following criteria for extrapolation to the 250 mg strength have been fulfilled:

- The formulations are dose-proportional
- The formulations are manufactured by the same manufacturer and manufacturing process
- Levofloxacin shows linear pharmacokinetics
- The *in vitro* dissolution results show similar profiles for the 250 mg and 500 mg strengths, with more than 85% dissolved within 15 minutes in pH 1.0, 4.5 and 6.8.

Design
A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 24 healthy (23 male and 1 female) subjects, aged 19-43 years. Each subject received a single dose (500 mg) of one of the 2 levofloxacin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was

continued for 4 h after dosing. For each subject there were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.75, 2, 2.25, 2.50, 3, 4, 6, 8, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study under fasting conditions to assess bioequivalence for levofloxacin is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects dropped out as they did not report for check in for Period II. 22 subjects completed the study and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levofloxacin under fasted conditions.

Treatment N=22	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	51.59 ± 7.69	53.58 ± 8.46	7.43 ± 1.49	0.92 (0.5 – 2.0)	7.7 ± 1.1
Reference	53.68 ± 7.49	55.74 ± 8.07	7.69 ± 1.73	1.17 (0.67 – 3.0)	7.7 ± 0.9
***Ratio (90% CI)**	0.96 (0.93 – 0.99)	--	0.97 (0.88 – 1.06)	--	--
CV (%)	6.8	--	18.0	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Levofloxacine Beximco 500 mg film-coated tablets is considered bioequivalent with Tavanic 500 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Beximco.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Convulsions • Psychotic reactions • QT interval prolongation

	• Hepatobiliary disorders • Renal impairment • Dysglycemia • Drug interactions • Vision disorders • Tendinitis and tendon rupture
Important potential risks	• Retinal toxicity • Pathogen resistance (including Methicillin-resistant *S. aureus* co-resistance and *E-coli* resistance) • Use in pregnant and lactating women
Missing information	• Use in children • Human data on *Bacillus anthracis* susceptibility

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 Tavanic. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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: a pilot test, followed by two rounds; 12 questions were asked. 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

Levofloxacine Beximco 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Tavanic 250 mg and 500 mg film-coated tablets. Tavanic is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Beximco with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 2015.

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