CBG MEB

Public Assessment Report

Scientific discussion

Levofloxacine Sandoz infuus 5 mg/ml, solution for infusion

(levofloxacin hemihydrate)

NL/H/3156/001/DC

Date: 23 May 2016

This module reflects the scientific discussion for the approval of Levofloxacine Sandoz infuus 5 mg/ml, solution for infusion. The procedure was finalised on 24 September 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
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 Sandoz infuus 5 mg/ml, solution for infusion, from Sandoz B.V.

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

- community-acquired pneumonia
- complicated skin and soft tissue infections

For the above-mentioned infections levofloxacin 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
- inhalation Anthrax: post exposure prophylaxis and curative treatment

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 IV, 5 mg/ml solution or infusion (NL License RVG 21810). Tavanic IV has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 9 December 1997 through mutual recognition procedure UK/H/0203/003.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Levofloxacine Sandoz infuus is a clear greenish-yellow solution for infusion, free from particles with approximately pH 4.8 and osmolality 280 - 340 mOsm/Kg.

Each ml of solution for infusion contains 5 mg of levofloxacin, as 5.12 mg/ml of levofloxacin hemihydrate.

The solution is packed in a 100 ml LDPE bag, filled with 50 ml or 100 ml solution for infusion.

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

II.2 Drug Substance

The active substance is levofloxacin hemihydrate, an active substance not described in the European Pharmacopoeia (Ph.Eur.). 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 product does not exhibit polymorphism.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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
Specified starting materials are converted to levofloxacin hemihydrate in 7 steps. The manufacturing process of both manufacturers is described in sufficient detail.

Quality control of drug substance
The drug substance specification of the MAH has been established in-house and is in line with the specifications of the ASMF-holders. The specification is acceptable.
Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer for 2 pilot scaled batches (manufacturer-I) and 1 pilot scaled batch (manufacturer-II) of the drug substance.

Stability of drug substance
Stability studies were conducted on three full scaled batches of each manufacturer stored at 25°C/60% RH (60 months), 30°C/65% RH (12 months; only the second manufacturer) and 40°C/75% RH (6 months). The results show that at long term and accelerated conditions all parameters comply with the proposed specification and no significant changes or trends has been observed. Based on the above observations a re-test period of 5 years can be granted. No special storage condition needed.

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 justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. In this development the same amounts of the active substance as well as the same quantitative composition compared to the innovator product is used. Hence, Levofloxacin Sandoz infuus 5 mg/ml solution for infusion has the same pharmaceutical form as the originator. Filtration and autoclaving are chosen as sterilization method. The MAH has adequately demonstrated that autoclaving does not affect the drug product. The sterility and bacterial endotoxin tests as per the requirements of European Pharmacopoeia monograph 2.6.1 and 2.6.14 are carried out at release and shelf-life. Since the product is administered intravenously it is not necessary to prove bioequivalence.

Manufacturing process
The manufacturing process includes dissolving of the raw materials, mixing, pH adjustment, filtration, forming filling and sealing of the bags, and post sterilization. The product is manufactured using conventional manufacturing techniques and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for six commercial scaled batches of 100 ml bags filled with 100 ml solution and three commercial scaled batches of 100 ml bags filled with 50 ml solution.

Control of excipients
All excipients used comply with the requirements of the Ph.Eur. 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 description, identification, pH, osmolality, assay, impurities, tightness, uniformity of dosage units, weight loss, bacterial endotoxins, sterility and particulate matter. 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 from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for 11 commercial scale batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 100 ml LDPE bags filled with 50 or 100 ml solution. Stability results showed no changes or trends in the parameters tested. A photostability study was performed and showed the product to be photosensitive. The proposed storage condition of "Keep the bag in the outer packaging in order to protect from light" is justified. An extra study was conducted under indoor light during 24 hours on the levofloxacin solution bag. No photosensitivity of the drug product was shown after 24 hours exposure to indoor light. Protection against light during infusion is not needed. The proposed shelf-life of 36 months is justified.

Compatibility with sodium chloride 0.9% solution, glucose 5% solution, glucose in 2.5% Ringer solution is shown. The in-use period for the reconstituted solutions is justified for 8 hours, without special conditions.

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 Sandoz infuus 5 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levofloxacine Sandoz infuus 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 IV 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

Levofloxacine hemihydrate 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

Levofloxacine Sandoz infuus 5 mg/ml, solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Levofloxacine Sandoz infuus 5 mg/ml is entirely the same as the originator. Therefore, it 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 Levofloxacine Sandoz infuus.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Drug interaction with cyclosporine
	• Tendinitis and tendon rupture
	• Muscular and ligament toxicity (rhabdomyolysis; muscle tear / rupture; ligament rupture)
	• Clostridium difficile-associated disease
	• Haemolytic reactions
	• Renal Impairment, Excretion reduction
	• Seizures in predisposed patients
	• Hypersensitivity reactions
	• Severe skin reactions: severe bullous reactions/ photosensitivity
	• Dysglycaemia
	• Neurotoxicity (Psychotic reactions/ Suicidality/ Peripheral neuropathy/ Seizures and Status Epilepticus)
	• Cardiac toxicity (prolonged QT interval/torsade de pointes)
	• Hepatotoxicity
	• Exacerbation of myasthenia gravis
	• Serious vision disorder
	• Drug interaction
	  ○ Ciclosporin
	  ○ Vitamin K antagonists

Important potential risks	• Toxicity to joints in children and growing adolescents • Lack of efficacy due to resistance development • Retinal detachment

Missing information	• Use in pregnancy and lactation

The MAH proposes routine risk minimisation measures through labeling in the SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. 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 IV 5 mg/ml solution for infusion. No new clinical studies were conducted. Levofloxacine Sandoz is a parenteral formulation and fulfils the requirements for an exemption from bioequivalence studies. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the registered innovator, Tavanic IV. Since the proposed PL is identical in wording and layout, the bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levofloxacine Sandoz infuus 5 mg/ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Tavanic IV 5 mg/ml solution for infusion. Tavanic IV is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 Sandoz infuus 5 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 September 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
Change of the currently registered batch size for a new batch size.	NL/H/3156/ IB/001/G	IB	2-12-2015	23-12-2015	Approval	No