CBG MEB

Public Assessment Report

Scientific discussion

Moxifloxacine VIOSER 400 mg/250 ml solution for infusion (moxifloxacin hydrochloride)

NL/H/3664/001/DC

Date: 1 May 2017

This module reflects the scientific discussion for the approval of Moxifloxacine VIOSER 400 mg/250 ml solution for infusion. The procedure was finalised on 28 November 2016. For information on changes after this date please refer to the module 'Update'.

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 Moxifloxacine VIOSER 400 mg/250 ml solution for infusion from Vioser S.A.

The product is indicated for the treatment of:

- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)

Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

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 Avelox 400 mg/250 ml solution for infusion (NL License RVG 28119) which has been registered in the Netherlands by Bayer B.V. since 2002 through mutual recognition procedure DE/H/0155/002 (original product).

The concerned member states (CMS) involved in this procedure was Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Moxifloxacine VIOSER 400 mg/250 ml is a clear yellow solution with pH between 4.4 and 4.6 and osmolality of 270 – 320 mOsm/kg. Each bottle of 250 ml contains 400 mg moxifloxacin (as hydrochloride). Each ml contains 1.745 mg moxifloxacin (as hydrochloride).

The solution is packed in low-density polyethylene bottles.

The excipients are: sodium acetate trihydrate, anhydrous sodium sulfate, acetic acid (for pH-adjustment), water for injections

II.2 Drug Substance

The active substance is moxifloxacin hydrochloride (anhydrous), an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a light yellow or yellow powder or crystals, slightly hygroscopic, and is sparingly soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone. The molecule possesses two stereogenic centers, with the pure S, S-enantiomer representing the selected configuration for the present development plan.

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

The manufacturing process of the active substance is covered by the CEP. Since water is used in the last step of the synthesis, and the drug product concerns a sterile, parenteral product it has been confirmed that the water used in the last step, complies with the quality criteria as described in the Note for Guidance on Quality of Water for Pharmaceutical Use.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. Monograph, with additional limits for several specified impurities that are not separately mentioned on the CEP or Ph. Eur., a separate limit for the isomer and additional limits for residual solvents. The additional test for residual solvents specifies more solvents than mentioned on the CEP and the proposed limits are acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches of the active substance.

Stability of drug substance
The active substance is stable for 60 months 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. Characterisation of the reference product was performed. The excipients used in the formulation are well known. No bioequivalence study has been performed. This is justified for the product. Compatibility of the drug product with the filters has been adequately demonstrated. A non standard sterilisation process is used which is adequately validated. Compatibility with the solutions has been adequately demonstrated.

Manufacturing process
The main steps in the manufacturing process are the preparation of the solution, sterile filtration and blow-fill-sealing of the bottles, capping and terminal sterilisation. The manufacturing process has been adequately described. Process validation data on the product has been presented for three consecutive batches. The batches are of the minimal commercial scale. As it concerns a standard process this is deemed acceptable.

Control of excipients
The excipients comply and are tested in accordance with their respective Ph. Eur. monographs. These specifications are acceptable.

Microbiological Attributes
The product is supplied as a single dose, sterile injectable solution. The applied terminal sterilisation process in the final container ensures conformity with the pharmacopoeial requirements for sterility and endotoxins. Pre sterilisation bioburden data also serve as evidence of the ruggedness of the process.

Quality control of drug product
The product specification includes tests for appearance, identification, pH, osmolality, extractable volume, uniformity of dosage units, assay, related substances, bacterial endotoxins, sterility, visible particles and sub-visible particles. The proposed release and end of shelf-life requirements are acceptable. Batch analytical data from the proposed production site have been provided on three commercial scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three commercial scaled batches stored at 25°C/40% RH (18 months), 30°C/35%RH (12 months) and 40°C/NMT25%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline for semi-permeable `1 containers. No trends or changes were observed for all stability conditions. A photostability study in accordance with the ICH Guideline on Photostability Testing showed that the product is slightly sensitive to light. On basis of the data submitted, the claimed shelf-life of 30 months with the storage condition: “Do not refrigerate or freeze, keep the bottle in the outer carton to protect from light”. The product should be used immediately after first opening and/or dilution.

Specific measures for the prevention of the transmission of animal spongiform encephalo-pathies
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 Moxifloxacine VIOSER 400 mg/250 ml 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 Moxifloxacine VIOSER 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 Avelox solution for infusion, 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

Moxifloxacin 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

Moxifloxacine VIOSER 400 mg/250 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 Moxifloxacine VIOSER 400 mg/250 ml is 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 Moxifloxacine VIOSER.

Summary table of safety concerns as approved in RMP

Important identified risks	- Hematological disorders (e.g. agranulocytosis, Prothrombin level increased) - Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions - Hypersensitivity/allergic reactions - Severe liver disorders - Serious bullous skin reactions - Photosensitivity reactions - Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea - Psychiatric reactions - Seizures and Patients predisposed to seizures (trigger of seizures) - Tendon inflammation/Tendon rupture - Peripheral neuropathy (paraesthesias, hypoaesthesias, dysaesthesias, or weakness) - Vision disorders - Patients with renal impairment (risk of renal failure due to dehydration) - Patients with myasthenia gravis (exacerbation of symptoms) - Patients with glucose-6-phosphate dehydrogenase deficiency - Patients on sodium diet - Peri-arterial tissue inflammation (in case of intra-arterial infusion) 18. INR decrease - Interference with biological tests
Important potential risks	- Rhabdomyolysis - Bradycardia - Off-label use in patients with MRSA Infections - Drug interaction with glibenclamid (theoretical risk of mild and transient hyperglycemia.
Missing information	- Off-label use in patients with special cSSSI (severe burn infections, fasciitis and diabetic foot infections with osteomyelitis) - Pregnancy - Use in children and growing Adolescents - lactating or nursing women (Safety not evaluated) - Off-label use in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN

The member states agree that routine pharmacovigilance is sufficient for moxifloxacin. No additional risk minimisation activities are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Avelox. No new clinical studies were conducted. The MAH demonstrated that the product is similar to the reference product based on chemical-pharmaceutical characteristics. 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 two rounds with 20 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Moxifloxacine VIOSER 400 mg/250 ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Avelox 400 mg/250 ml solution for infusion. Avelox 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 Moxifloxacine VIOSER with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 November 2016.

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