COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Moxifloxacine MSN 400 mg film-coated tablets

(moxifloxacin hydrochloride)

NL/H/4360/001/DC

Date: 4 September 2019

This module reflects the scientific discussion for the approval of Moxifloxacine MSN. The procedure was finalised on 8 May 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 Moxifloxacine MSN 400 mg film-coated tablets from Vivanta Generics s.r.o.

Moxifloxacine MSN 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin (see sections 4.4, 4.8 and 5.1 of the SmPC).

- Acute bacterial sinusitis (adequately diagnosed)
In acute bacterial sinusitis moxifloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

- Acute exacerbations of chronic obstructive pulmonary disease including bronchitus
In acute exacerbations of chronic obstructive pulmonary disease including bronchitis moxifloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- Community acquired pneumonia, except severe cases
- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

Moxifloxacine MSN 400 mg film-coated tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of *Neisseria gonorrhoeae* unless moxifloxacinresistant *Neisseria gonorrhoeae* can be excluded (see sections 4.4 and 5.1 of the SmPC).

Moxifloxacine MSN 400 mg film-coated tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:
- Community-acquired pneumonia
- Complicated skin and skin structure infections

Moxifloxacine MSN 400 mg film-coated tablets should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

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 Avalox 400 mg, film-coated tablets which has been registered in Germany by Bayer Vital GmbH since 21 June 1999. In the Netherlands, Avelox 400 mg (NL License RVG 28118) has been registered by Bayer B.V. since 17 October 2002 through mutual recognition procedure DE/H/0155/002.

The concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Poland, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Moxifloxacine MSN 400 mg is a dull red coloured, caplet shaped film-coated tablet debossed with “M” on one side and “400” on the other side. Each film-coated tablet contains 400 mg moxifloxacin (as hydrochloride).

The film-coated tablets are packed in clear PVC/PVdC- Aluminium blisters.

The excipients are:
tablet core - lactose monohydrate, povidone K29/32, lactose anhydrous, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate
film-coating - Opadry Brown 03B86891: hypromellose 2910, 6 mPa.s E464, titanium dioxide E171, macrogol 400, ferric oxide red E172

II.2 Drug Substance

The active substance is moxifloxacin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a light yellow to yellow powder or crystals. It is sparingly soluble in water.

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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the Ph.Eur. and the CEP, with additional requirements for particle size and microorganisms. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

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. The MAH has performed many attributes from Quality-by-Design during pharmaceutical Development. Comparative dissolution data in several physiological pH shows that the dissolution characteristics of the proposed product are comparable to the dissolution characteristics of the innovator product. Hence, these studies support the results obtained in the bioequivalence study.

Manufacturing process
The intra-granulate ingredients of the tablets are sifted, followed by dry mixing and granulation. After drying of the granulate, the granules are sifted and milled, and the extra granulate excipients are added and the mixture is mixed again. Magnesium stearate is then added as lubricant. Next, the tablets are compressed and coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches.
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur. and in-house requirements where there is no Ph. Eur. monograph. The proposed excipient specifications are deemed adequate. The MAH has adequately discussed and adopted Ph. Eur. functionality related characteristics as appropriate.

Quality control of drug product
The product specification includes tests for description, identification (active substance and colourant), average mass, uniformity of dosage units, disintegration, water, dissolution, assay, related substances, and microbiological examination. The release and shelf-life

requirements/limits are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on pilot-scale batches, demonstrating compliance with the release specification.
The product specifications cover appropriate parameters for this dosage form. Furthermore, the proposed dissolution limit is acceptable in view of the reflection paper on Dissolution Specification for Generic Oral Immediate Release Products.

Stability of drug product
Stability data on the product has been provided three pilot-scale batches stored at 25°C/60% RH (36 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 blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. There was no change in any of the parameters observed during the stability studies.
The proposed shelf-life of 36 months when packed in blister, with storage condition "This medicinal product does not require any special storage conditions" is acceptable.

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 Moxifloxacine MSN 400 mg film-coated tablets 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 MSN 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 Avalox, 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 hydrochloride 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Moxifloxacine MSN 400 mg (Vivanta Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Avalox 400 mg film-coated tablets (Bayer Vital GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-43 years. Each subject received a single dose (400 mg) of one of the 2 movifloxacin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at -dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting conditions applied in the study 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
All 28 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of moxifloxacine under fasted conditions

Treatment N=28	**AUC_{0-t}** (µg.h/ml)	**$AUC_{0-\infty}$** (µg.h/ml)	**C_{max}** (µg/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	50.2 ± 7.5	52.1 ± 7.7	4.7 ± 1.3	1.25 (0.5 – 3.0)	14 ± 3
Reference	50.5 ± 6.5	52.5 ± 6.6	4.4 ± 0.9	1.5 (0.5 – 3.5)	14 ± 2
***Ratio (90% CI)**	0.99 (0.98-1.01)	--	1.06 (0.98-1.14)	--	--
CV (%)	3.2	--	16.0	--	--

$AUC_{0-\infty}$ 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 Moxifloxacine MSN 400 mg is considered bioequivalent with Avalox 400 mg film-coated tablets.

Safety
A total of 8 adverse events (AEs) were observed in the study. Out of 8 AEs, 5 (17.86%) AEs were reported in the test arm and 3 (10.71%) AEs were reported in the reference arm.
The adverse events observed in this study were in line with the known safety profile of the product and were mild in severity. No serious adverse events were observed in in this study. Both test and reference formulations are well tolerated by subjects in this study and comparable in relation to safety aspects.

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 Moxifloxacine MSN.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Serious haematological disorders • Hypersensitivity, anaphylaxis • Tendinopathy • Prolongation of QTc interval • Hepatotoxicity • Serious bullous skin reactions • Seizure • Peripheral neuropathy • Depression, suicidality and psychosis • Antibiotic associated diarrhoea (including colitis) in hospital setting • Exacerbation of myasthenia gravis • Renal failure • Serious vision disorder
Important potential risks	• Bradycardia • Rhabdomyolysis, myositis and myopathy • Muscle rupture • Ligament rupture • Selection of drug resistant isolates
Missing information	• Arthropathy (in paediatrics patients) • Use of moxifloxacin in children and growing adolescents

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 Avalox. 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 (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. The test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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

Moxifloxacine MSN 400 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Avalox 400 mg, film-coated tablets. Avalox 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 Moxifloxacine MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 May 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