

Public Assessment Report

Scientific discussion

**Moxifloxacin Fresenius Kabi 400 mg/250 ml
solution for infusion
(moxifloxacin hydrochloride)**

NL/H/2807/001/DC

Date: 12 May 2014

This module reflects the scientific discussion for the approval of Moxifloxacin Fresenius Kabi 400 mg/250 ml. The procedure was finalised on 27 November 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Moxifloxacin Fresenius Kabi 400 mg/250 ml solution for infusion from Fresenius Kabi Nederland BV.

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

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Germany, Finland, Hungary, Ireland, Italy, Luxembourg, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Moxifloxacin Kabi 400 mg/250 ml is a clear yellow solution with pH between 5.0 and 6.0 and osmolality of 260 – 330 mOsm.

The solution is either packed in low-density polyethylene bottles closed with a cap containing a rubber disc to allow insertion of the needle, or in polyolefine bags with an administration port (infusion port) and addition port (injection port) consisting of a polypropylene housing and an aluminium-overpouch.

Each bottle or bag of 250 ml contains 400 mg moxifloxacin (as hydrochloride). Each ml contains 1.6 mg moxifloxacin (as hydrochloride).

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

II.2 Drug Substance

The active substance is moxifloxacin hydrochloride (anhydrous), an established 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 and practically insoluble in acetone.

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

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

Quality control of drug substance

In addition to the requirements for moxifloxacin hydrochloride described in the monograph of the Ph.Eur. and the current CEP, the following microbiological tests are performed: bacterial endotoxins and total aerobic microbial count and total combined yeasts and moulds. Batch analysis data on three batches is provided. The MAH has indicated that the Ph.Eur. reference standard is used as primary reference standard. This is acceptable.

Stability of drug substance

Stability data are provided on 7 batches stored at 25°C/60%RH (up to 60 months) and 40°C/75%RH (6 months). Under both accelerated and long term conditions no up- or downward trends are observed for any of the parameters tested. Hence it can be concluded that the drug substance is stable. The proposed re-test period of 60 months without specific storage condition can be granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Although moxifloxacin hydrochloride is sparingly soluble in water it is soluble in an adequate acidic medium. The development studies performed were regarding characterisation of the innovator product, optimization of the formulation to obtain an isotonic solution with the right pH, stability studies at temperatures of 5°C, 25°C, 30°C and 40°C up to 6 months, a photostability study, exposure to up to three autoclave cycles and heat sensitivity studies. The excipients used in the product are well known. No overages are used. The drug product is sterilised in the final container. The integrity of the different container types is tested regularly with a microbiological integrity test. The product does not contain any antimicrobial preservatives. The choices of the packaging and manufacturing process are justified.

Manufacturing process

The drug product is packed in two different primary packaging materials at different manufacturing sites. The manufacturing process of the polyolefin bags differs slightly from that of the polyethylene bottles. The main steps in the manufacturing process are the preparation of the solution, sterile filtration and filling of the solution into the primary packaging. The main difference between the sites/packs is in the filling part. The bags are thermally sterilized using Pharmacopoeial conditions. The bottles are filled by blow-fill-seal technique and are then thermally sterilized using non-Pharmacopoeial sterilization parameters.

Process validation data on the product have been presented for three pilot-scale batches for the bags and for one full-scale and two pilot-scale batches for the bottle pack. Process validation for full-scale batches for the product in bags (standard process) will be performed post authorization.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for clarity, degree of colouration, pH, osmolality, extractable volume (release limit), weight loss (shelf-life limit), identification, assay, related substances and microbial quality. Except for assay and total degradation products, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three batches per presentation.

Stability of drug product

Stability data on both presentations of the product have been provided for three production-scale batches. These were stored at 25°C/40% RH, 30°C/35%RH and 40°C/NMT 25%RH up to 12 months. The conditions used in the stability studies are in accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in semi-permeable containers. All batches comply with the proposed set of specifications, at all temperatures tested. The only visible trend is the temperature dependent increase in weight loss, which is common for these type of packages. Data on photostability of the drug product were included in the development section, where it was shown that the drug product should be protected from light. The proposed shelf-life of 24 months is justified. The storage conditions are 'Do not refrigerate or freeze' and 'Keep the bottle in the outer carton in order to protect from light'.

The compatibility of the product was tested with the following solutions: Water for injections, Dextrose 5%, Dextrose 10%, Sodium Chloride (0.9% w/v), Ringer solution and Ringer Lactate solution. The mixture ratio was 1:1. The samples were tested according to shelf-life specification with the exception of the parameters weight loss and microbiological requirements. It has been demonstrated that the product is compatible and physico-chemically stable with the tested standard infusion solutions over a period of 24 hours at 25°C.

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 Moxifloxacin Kabi 400 mg/250 ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH will continue the (stability) studies not yet completed according to the study design until the end of shelf-life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Moxifloxacin Kabi 400 mg/250 ml, solution for infusion 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

Biowaiver

Moxifloxacin Fresenius Kabi 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 Moxifloxacin Fresenius Kabi 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 Moxifloxacin Fresenius Kabi 400 mg/250 ml.

Summary table of safety concerns as approved in RMP

Important identified risks	- Serious hematological disorders (e.g. agranulocytosis, hemolytic anemia) - QTc interval prolongation - Severe liver disorders - Serious bullous skin reactions - Photosensitivity reactions - Antibiotic-associated diarrhea incl. pseudomembranous colitis - Psychiatric reactions - Hypersensitivity/Allergic reactions - Tendon inflammation/Tendon rupture - Peripheral neuropathy - Vision disorders - Patients with renal impairment (risk of renal failure due to dehydration) - Patients predisposed to seizures (trigger of seizures) - 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 intraarterial infusion) - Drug interaction resulting to QTc-interval prolongation, ventricular arrhythmias, incl. torsade de pointes - INR decrease (increase in oral anticoagulant activity) - Interference with biological tests
Important potential risks	- Rhabdomyolysis - Myositis/Myopathy - Peripheral neuropathy - Bradycardia - Selection of drug resistant isolates - Off-label use in patients with special cSSSI (severe burn infections, fasciitis and diabetic foot infections with osteomyelitis) - Off-label use in patients with MRSA infections - Pediatric population (cartilage lesions) - Drug interaction with glibenclamid (theoretical risk of mild and transient hyperglycemia)
Missing information	- Use together with QTc prolonging drugs or concurrent risk factors for QTc prolongation

	- Use in children and growing adolescents - Arthropathy (in pediatric patients) - Neonates and premature neonates - Pregnant and lactating women (Safety not evaluated) - Off-label use in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN
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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 solution for infusion 400 mg/250 ml. 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 pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers.

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

Moxifloxacin Fresenius Kabi 400 mg/250 ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Avelox solution for infusion 400 mg/250 ml. 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 Moxifloxacin Fresenius Kabi 400 mg/250 ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 November 2013.

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