COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Flucloxacilline Fresenius Kabi 250 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion

(flucloxacillin sodium)

NL/H/4776/001-004/DC

Date: 26 November 2020

This module reflects the scientific discussion for the approval of Flucloxacilline Fresenius Kabi. The procedure was finalised on 3 September 2020. 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 Flucloxacilline Fresenius Kabi 250 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion from Fresenius Kabi Nederland B.V.

The product is indicated for the treatment of the following infections due to beta-lactamase-producing staphylococci and other sensitive Gram-positive organisms such as streptococci (see section 4.2 and 5.1 of the SmPC):

- Skin and soft tissue infections like abscesses, cellulitis, infected burns, impetigo
- Upper respiratory tract infections, like pharyngitis, tonsillitis, sinusitis
- Lower respiratory tract infections, like pneumonia, bronchopneumonia, pulmonary abscess
- Bone and joint infections like osteomyelitis and arthritis
- Endocarditis
- Prophylaxis in cardiovascular surgery (valve prostheses, artery prostheses) and in orthopedic surgery (arthroplasty, osteosynthesis and arthrotomy)

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 Floxapen powder for solution for injection 250 mg, 500 mg and 1 g (NL Licence RVG 05990) which has been registered in the Netherlands by Aurobindo Pharma B.V. since 14 January 1971. The European Reference Product for this formulation is Floxapen 2000 mg powder for solution for injection/infusion, registered in Belgium.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Ireland, Portugal, Slovakia and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Flucloxacilline Fresenius Kabi is a fine white or almost white, hygroscopic, crystalline sterile powder for solution for injection/infusion.
It is available in four strengths: 250 mg, 500 mg, 1000 mg and 2000 mg flucloxacillin (as flucloxacillin sodium). The drug product only contains the active substance and contains no excipients. The powder is packed in 10 ml (250 and 500 mg), 20 ml (1000 mg) and 50 ml (2000 mg) glass type II vials closed with chlorobutyl or bromobutyl rubber stoppers. To clearly distinguish between the different product strengths different colour flip-off caps are used.

II.2 Drug Substance

The active substance is sterile flucloxacillin sodium, an established active substance described in the European Pharmacopoeia. The active substance is a white or almost white, hygroscopic, crystalline powder and is freely soluble in water and in methanol, and soluble in ethanol. Flucloxacillin sodium shows optical rotation due to the presence of three asymmetric carbons. The physicochemical characterisation of polymorphism is not relevant for the current product. As the product is dissolved, there is no effect of polymorphs on the bioavailability.

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 additional information is required. However, filter bacterial challenge validation data, including viability study has been provided.

Quality control of drug substance
The active substance specification is in line with the CEP except for one test and a number of additional requirements. These have been adequately justified. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 36 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 absence of excipients is justified. The choices of the packaging and manufacturing process are justified in relation to the innovator. No detailed description has been provided on the development of the formulation. The composition of the drug product is identical to the reference product. As the drug product is a powder for solution consisting of only the active substance based on a registered product, no further information is required regarding the formulation development.

Manufacturing process

Due to the experience of the manufacturer the manufacturing process is considered to be a standard process. It consists of one basic step: aseptic filling of the sterile drug substance directly into pre-sterilised vials closed with pre-sterilised rubber stoppers.
Process validation data on the product has been presented for two pilot scaled batches of 250 mg, one pilot scaled and two full scaled batches of 500 mg, three full scaled batches of 1000 mg and two pilot and one full scaled batch of 2000 mg.

Quality control of drug product

The product specification includes tests for appearance of powder, appearance of solution, pH, water, uniformity of dosage units, identification, assay, related substances, sub-visible particles, visible particles, sterility, bacterial endotoxins and reconstitution time. The release and shelf-life limits are identical. A risk evaluation for nitrosamines has been performed and no risk of presence of nitrosamines was identified.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot scale batches of 250 mg, one pilot scale and two full scaled batches of 500 mg, three full scaled batches of 1000 mg and two pilot and one full scaled batch of 2000 mg.

Stability of drug product

Stability data on the product has been provided on two production scaled batches of 250 mg, 500 mg and 1000 mg, and three production scaled batches of 2000 mg stored at 40°C/75% RH (6 months) and 25°C/60% RH (250, 500, 1000 mg: 24 months; 2000 mg: 18months) and 30°C/65% RH (250, 1000 mg: 24 months; 2000 mg: 18 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type II glass vials and bottles. The results show no out of specifications or significant changes at the tested storage conditions. No difference between batches with chlorobutyl rubber stopper or bromobutyl rubber stopper are observed. Hence, both stoppers are acceptable.
Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The proposed shelf life of 24 months for the 250, 500 and 1000 mg and 2000 mg product without any specific storage condition has been granted.

In-use shelf-life
Stability data has been provided. The compatibility of the drug product after reconstitution/dilution with the diluents prescribed in the SmPC was investigated at 2-8°C (24 hours) and 20-25°C (2 hours) in different packaging materials. Based on the data presented, it can be concluded that the chemical and physical in-use stability of reconstituted or further diluted product has been demonstrated for 2 hours at 20-25 °C and for 24 hours at 2-8 °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 Flucloxacilline Fresenius Kabi 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 Flucloxacilline Fresenius Kabi 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 Floxapen 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

Flucloxacillin sodium 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

Flucloxacilline Fresenius Kabi 250 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/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 Flucloxacilline Fresenius Kabi 250 mg, 500 mg, 1000 mg and 2000 mg 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 Flucloxacilline Fresenius Kabi.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity to β-lactams & anaphylaxis - Hepatitis & cholestatic jaundice - Neurotoxicity in severe renal failure (convulsions) - Hyperbilirubinaemia in newborns - Overgrowth of non-susceptible organisms with prolonged use - Neutropenia (including agranulocytosis) - Severe skin reactions (EM, SJS & TEN)
Important potential risks	- Use in patients on sodium restriction - Use in patients with phenylketonuria - Reduced therapeutic effect of flucloxacillin on concomitant use with bacteriostatic drugs - Reduced efficacy of combined oral contraceptives
Missing information	- Use in pregnant & lactating women

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 Floxapen. 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

Flucloxacilline Fresenius Kabi 250 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Floxapen. Floxapen is a well-known medicinal product with an established favourable efficacy and safety profile.

Equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes.

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 Flucloxacilline Fresenius Kabi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on on 3 September 2020.

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