COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cefuroxim Fresenius Kabi 1500 mg, powder for solution for infusion (cefuroxime sodium)

NL/H/4763/001/DC

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Cefuroxim Fresenius Kabi 1500 mg, powder for solution for infusion. The procedure was finalised on 16 October 2008 in Germany (DE/H/0914/001DC). After a transfer on 25 February 2019, the current RMS is the Netherlands. 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
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMS	Reference Member State
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 Cefuroxim Fresenius Kabi 1500 mg, powder for solution for infusion, from Fresenius Kabi Nederland BV.

The product is indicated for the treatment of bacterial 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 Zinacef 1500 mg, powder for solution for infusion, which has been registered in Germany by GlaxoSmithKline GmbH&Co. KG since 6 November 1982 under the de procedure number 334.04.00.

The reference member state (RMS) of the initial procedure was Germany and the concerned member states (CMS) were Belgium, Finland, France, the Netherlands and Spain. The role of RMS was transferred to the Netherlands on 25 February 2019.

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

II. QUALITY ASPECTS

II.1 Introduction

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. A signed declaration of the qualified person, that cefuroxime sodium is manufactured in compliance with the guidelines on GMP for active substances, has been given.

II.2 Drug Substance

The active substance cefuroxime sodium is a semi-synthetic second-generation broad-spectrum cephalosporin antibiotic for parenteral administration.

Manufacturing process

A CEP is provided. Thus, as the drug substance is supplied sterile, only the sterilisation process is described in the dossier as part of the manufacture of cefuroxime sodium.

Quality control of drug substance

The tests for residual solvents and sterility are performed by the drug substance manufacturer only. The incoming drug substance is checked visually for integrity of the packaging material (stoppered aluminium tins) in order to ensure sterility of the drug substance. The specifications are considered suitable for use in the drug product applied for. Batch analysis data presented show compliance with the Ph.Eur. requirements and the additional specifications.

Stability of drug substance

As the discrepancies in mass balance seen in the stability data for the drug substance could not be solved, a re-test period is not foreseen for the drug substance. Testing as per specification before use in the manufacture of the drug product was confirmed. The documentation for Cefuroxime sodium including sterilisation procedure is adequately drawn up.

II.3 Medicinal Product

Pharmaceutical development

The drug product is a powder for solution for infusion filled in type II glass bottles. The information about the packaging material is considered sufficient. Only one type of stopper will be used for the drug product routinely. The compatibility with the solutions stated in the SmPC to be compatible is tested.

Manufacturing process

The sterile cefuroxime sodium powder is filled into the containers under nitrogen atmosphere. The manufacture of the finished product is adequately described. The product specification cover appropriate parameters for this dosage forms.

Quality control of drug product

For release and stability testing of assay and related substances a sufficient HPLC method is described and fully validated. It has been demonstrated that the Ph.Eur. method does not allow proper differentiation between impurities. Validation data for bacterial endotoxins and sterility are provided, too. Batch analysis has been performed on at least two batches per drug product applied for. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product

All relevant parameters have been tested during stability studies. Stability data (up to 12 months have been provided) from recently produced batches show compliance with the proposed specifications. A slight decrease of the assay of Cefuroxime is accompanied by a plausible increase of total impurities. Extrapolation of data to establish the claimed shelf-life of 24 months is considered acceptable. Based on the originator's SmPC, the storage recommendation "Do not store above 25°C" is given. This is deemed acceptable as the substance is sensitive to elevated temperatures. An in-use storage period of 5 hours is claimed and justified by sufficient data. For the in-use storage period a separate specification

considered suitable and sufficiently qualified is established. The conditions and test frequencies used in the stability studies are according to the ICH stability guideline.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cefuroxime are well known. As cefuroxime is a widely used, well-known active substance, no further studies are required and the MAH provides none. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cefuroxime sodium is a broad spectrum, 2nd-generation cephalosporin for parenteral use in various indications in adults, adolescents and children approved for the originator product since 1982. It has activity against a wide range of common Gram-positive and Gram-negative pathogens including beta-lactamase producing strains and some anaerobes.

The applicant submitted a clinical overview which is acceptable.

IV.2 Pharmacokinetics

The pharmacokinetics of cefuroxime are well known. The applicant amended data for all PK-parameters (according to the requests of the SmPC-guideline) in section 5.2 of the SmPC.

IV.3 Pharmacodynamics

Pharmacodynamic properties are well known. Resistance data of the indication relevant pathogens are surveyed and regularly updated. These data have been extensively elaborated by the applicant also considering the resistance situation in the CMS and have been included in the SmPC.

IV.4 Clinical efficacy

The list of indications is considered acceptable.

IV.5 Clinical safety

None.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the application for Cefuroxim Fresenius Kabi 1500 mg, powder for solution for infusion, in the treatment of bacterial infections (for details see SmPC), is approved.

For intermediate amendments see current product information.

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
NL/H/4763/ 1/IA/015	Updated (CEP) certificate from an already approved manufacturer.	No	15-4-2020	Approved	N/A
NL/H/4763/ 1/IB/016	Revise the warning related to sodium in the package leaflet (PL) and SmPC.	Yes	12-12-2020	Approved	N/A
NL/H/4763/ 1/IA/017/G	Updated (CEP) certificate from an already approved manufacturer.	No	28-2-2022	Approved	N/A
NL/H/4763/ 1/IB/018	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance: change in the testing frequency of a residual solvent and editorial changes.	No	3-8-2022	Approved	N/A