CBG MEB

Public Assessment Report

Scientific discussion

Cefuroxim SUN 250 mg and 500 mg, film-coated tablets

(cefuroxime axetil)

NL/H/3434/001-002/DC

Date: 30 June 2016

This module reflects the scientific discussion for the approval of Cefuroxim SUN 250 mg and 500 mg, film-coated tablets. The procedure was finalised on 29 October 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Cefuroxim SUN 250 mg and 500 mg, film-coated tablets from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for the treatment of the infections listed below in adults and children from the age of 3 months

- Acute streptococcal tonsillitis and pharyngitis
- Acute bacterial sinusitis
- Acute otitis media
- Acute exacerbations of chronic bronchitis
- Cystitis
- Pyelonephritis
- Uncomplicated skin and soft tissue infections
- Treatment of early Lyme disease

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 Zinnat 250 mg and 500 mg film-coated tablets (NL RVG license numbers 13226 and 13227) which has been registered in The Netherlands by GlaxoSmithKline B.V. since 17 March 1989.

The concerned member states (CMS) involved in this procedure were the Czech Republic, Germany, Hungary, Poland and the Slovak Republic. For Cefuroxim SUN 500 mg, film-coated tablets, Spain was an additional concerned member state.

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

II. QUALITY ASPECTS

II.1 Introduction

Cefuroxim SUN 250 mg is a white to off white film-coated modified capsule shaped tablet debossed with “250” on one side and plan on the other side. Each tablet contains 250 mg cefuroxime which is equivalent to 300.7 mg cefuroxime axetil.
Cefuroxim SUN 500 mg is a white to off white film-coated modified capsule shaped tablet debossed with “500” on one side and plan on the other side. Each tablet contains 500 mg cefuroxime which is equivalent to 601.4 mg cefuroxime axetil.

The film-coated tablets are packed in PVC/Aclar/Al blisters.

The excipients are:
tablet core – microcrystalline cellulose (PH101), microcrystalline cellulose (PH112), croscarmellose sodium, sodium lauryl sulphate, hydrogenated vegetable oil and silica colloidal anhydrous.
film coating – opadry white OY-S-58910 containing: hypromellose (E464), titanium dioxide (E171), macrogel (E1521) and talc (E553b).

The two strengths are fully dose proportional.

II.2 Drug Substance

The active substance is cefuroxime axetil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder. Cefuroxime axetil is soluble in acetone, ethyl acetate and methanol, very slightly soluble in aqueous media and has pH independent solubility

in the physiological pH range. The active substance is a mixture of two diastereoisomers. It exists both in crystalline and amorphous forms, the latter is used in this formulation.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. A crystallinity test was performed in order to confirm that the drug substance is in an amorphous form. Batch analytical data demonstrating compliance with this specification have been provided for four 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The formulation development of the product has been described, the choice of excipients is justified and their functions explained.

Comparative dissolution data between the two batches used in the bioequivalence study in three different media (0.1N HCl, pH 4.5 and pH 6.8), were provided. While the products showed similar dissolution in pH 4.5 and pH 6.8 , their profiles differed in 0.1N HCl. The reason for this discrepancy is most likely due to a difference in the composition between the test and reference product. This issue is not pursued as bioequivalence has been established.

In addition *in vitro* dissolution tests were provided in support of a biowaiver. The dissolution results of the 250 mg and 500 mg tablet obtained in three different buffers (0.1 N HCl, pH 4.5 and pH 6.8) were similar.

Manufacturing process
A dry granulation manufacturing process is used and consists of sifting, milling, mixing, blending, compression, film-coating and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three test batches of common blend and three test batches of each strength, in accordance with the relevant European guidelines.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, uniformity of dosage units by mass variation, dissolution, water, related substances, assay and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three bathes of each strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months).The product was stored in the proposed packaging. The conditions used in the stability studies are according to the ICH stability guideline. The results of the photostability studies show that the product is photo stable and does not undergo degradation. On basis of the data submitted, a shelf life was granted of 24 months.

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 Cefuroxim SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
The following post-approval commitments have been made during the procedure:

- That all the commercial batches will be tested against EPCRS as primary reference standard or using working standard which has been standardised against EPCRS.
- To re-evaluate the end of shelf life limit for anti cefuroxime axetil when complete stability data is available.
- To re-evaluate the release and end of shelf life limit for total impurities when complete stability data is available.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cefuroxim SUN 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 Zinnat 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

Cefuroxime axetil 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 Cefuroxim SUN 500 mg, tablets (Ranbaxy Laboratories Limited, India) is compared with the pharmacokinetic profile of the reference product Zinnat 500 mg tablets (GlaxoSmithKline, UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. Furthermore the bioequivalence batches are of sufficient size in relation to the intended commercial batch size.

Biowaiver

The MAH has carried out a bioequivalence study on the highest strength (500 mg). The results of this study can be extrapolated to the lower strength, as the criteria for biowaiving have been fulfilled:

- The tablets are dose proportional
- The tablets are manufactured by the same manufacturer and manufacturing process
- Over the 125–1000 mg dose range, cefuroxime shows linear pharmacokinetics
- Dissolution at pH 1.2, 4.5 and 6.8 shows comparable dissolution

Bioequivalence study

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-40 years. Each subject received a single dose (500 mg) of one of the 2 cefuroxime axetil formulations. The tablet was orally administered with 240 ml water, 30 minutes after the start of intake of a high fat, high calorie, standard breakfast (whole bread, 2 fried eggs, fillet, butter, cheddar cheese and yoghurt). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.50, 0.75, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 4.333, 4.667, 5.0, 5.500 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0 and 24.0 hours after administration of the products.

The design of the study is acceptable.

A study under fed conditions is considered adequate considering the method of administration mentioned in the SmPC is: ‘Cefuroxim SUN should be taken after food for optimum absorption’.

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. The data on cefuroxime were taking into account, as cefuroxime axetil is a prodrug which is very rapidly converted into cefuroxime. This is acceptable.

Results

Of the 28 subjects, one subject was withdrawn before the start of the study, because of non-compliance with the study requirements. Therefore, 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cefuroxime under fed conditions.

Treatment N=27	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h	$t_{1/2}$ h
Test	31.3 ± 6.0	31.4 ± 6.0	7.88 ± 1.71	4.1 ± 1.4	1.4 ± 0.2
Reference	30.8 ± 6.9	30.9 ± 6.9	7.45 ± 1.96	3.5 ± 1.4	1.5 ± 0.3
***Ratio (90% CI)**	1.02 (0.99 – 1.06)	--	1.06 (0.97 – 1.16)	--	--

CV (%)	7.0	--	19.1	--	--

$AUC_{0-\infty}$ 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 the bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Cefuroxime SUN 500 mg, tablet is considered bioequivalent with the Zinnat 500 mg tablet.

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).

The results of study TR-024-CEFUR-12 with 500 mg formulation can be extrapolated to other strength 250 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 Zinnat 250 mg and 500 mg film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions o angioedema, anaphylaxis, serum sickness, drug fever o serious skin reactions: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) - Severe haematological reactions (e.g. leukopenia, thrombocytopenia, haemolytic anaemia)
Important potential risks	- Liver impairment - Bacterial resistance - Use during lactation
Missing information	- Effect on fertility - Use during pregnancy and lactation - Use in patients with hepatic impairment - Use in children under the age of 3 months.

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 Zinnat. 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 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. 24 subjects were questioned: 4 during the preliminary round of testing, and 2 groups of each 10 persons during the following 2 test rounds.
A questionnaire of 15 questions on the leaflet content was used, sufficiently addressing the key safety and usage messages, and 3 additional questions to obtain feedback on the format of the leaflet. General and applicability questions were used to investigate the technical readability, comprehensibility of the text, traceability of the information and the applicability. During both test rounds information was located and understood by all subjects for all questions. The package leaflet is well structured and organised, easy to understand and written in a comprehensible manner.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cefuroxim SUN 250 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zinnat 250 mg and 500 mg film-coated tablets. Zinnat 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 Cefuroxim SUN 250 mg and 500 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 October 2015.

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