

## **Public Assessment Report**

### **Scientific discussion**

**Cefuroxim Mylan 250 mg and 500 mg,  
film-coated tablets**

**(cefuroxime axetil)**

**NL/H/4371/001-002/DC**

**Date: 23 August 2019**

This module reflects the scientific discussion for the approval of Cefuroxim Mylan 250 mg and 500 mg, film-coated tablets. The procedure was finalised at 26 June 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
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 Mylan 250 mg and 500 mg, film-coated tablets from Mylan Ireland Limited.

The product is indicated for the treatment of the infections listed below in adults and children from the age of three 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 license RVG 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 France, Italy, Poland and Slovakia.

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

## II. QUALITY ASPECTS

### II.1 Introduction

Cefuroxim Mylan is a white to off-white capsule shaped film-coated tablet in two strengths:  
*250 mg strength* - 'A 33' debossed on one side and plain on the other side. Each tablet contains 250 mg cefuroxime which is equivalent to 300.7 mg cefuroxime axetil.  
*500 mg strength* - 'A 34' debossed on one side and plain 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 blister packs.

The excipients are microcrystalline cellulose, sodium croscarmellose, sodium lauril sulfate (E487), colloidal anhydrous silica, hydrogenated vegetable oil, hypromellose, titanium dioxide (E171), and macrogol.

The two tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is cefuroxime axetil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Cefuroxime axetil is a white or almost white powder. It is slightly soluble in water, soluble in acetone, in ethyl acetate and in methanol, and slightly soluble in alcohol. The amorphous form is manufactured.

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. The MAH deviates from the methods and procedures as stated in the Ph.Eur. monograph on cefuroxime axetil. Additional data have been provided which demonstrate that similar results are obtained with the proposed in-house methods compared to the Ph.Eur. The described analytical methods and their validation are adequate for the intended use. Batch analytical data demonstrating compliance with this specification have been provided for six 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 choice of excipients is

justified and their functions explained. Initially, uncoated tablets were produced. However, due to the bitter taste of the tablets, a film-coating was added to the formulation. The MAH has justified the proposed tablet sizes and formulation for use, by making comparisons with the reference product, which is acceptable as per the Guideline on Pharmaceutical Development of Medicines for Paediatric Use. The pharmaceutical development of the product has been adequately performed.

The results of one bioequivalence study using the 500 mg strength have been submitted. Comparative dissolution studies were performed to support the results obtained in the bioequivalence study as well as the biowaiver of strength for the 250 mg tablets. As the bioequivalence study was performed with uncoated tablets, the MAH has also performed additional comparative dissolution studies in three different pH conditions to show that the film-coated tablets have similar dissolution characteristics as the uncoated tablets. Comparable dissolution results are obtained with the coated and uncoated tablets. The change in composition from uncoated to film-coated tablets is minor and not expected to affect bioavailability from a quality point of view.

#### Manufacturing process

The selected manufacturing process is dry granulation. The manufacturing process is clearly described. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient batches in accordance with the relevant European guidelines.

#### Control of excipients

The proposed excipient specifications are deemed acceptable as excipients are tested according to 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 description, identification, average weight, uniformity of dosage units, dissolution, related substances, assay, water, thickness, identification of titanium dioxide, and microbial contamination. 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 of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

#### Stability of drug product

The results of stability studies according to the ICH stability guideline have been provided. Three batches of the 250 mg film-coated tablets and three batches of the 500 mg film-coated tablets were placed on stability. Tablets were stored in the proposed packaging for 36 months at long term storage conditions (25°C/60% RH) and for six months at accelerated

storage conditions (40°C/75% RH). No clear trends or out-of-specification results were observed. On basis of the data submitted, a shelf life was granted of 36 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 Mylan 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 Cefuroxim Mylan 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 one 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 Mylan 500 mg tablets (Mylan Ireland Limited, Ireland) is compared with the pharmacokinetic profile of the reference product Zinnat 500 mg tablets (GlaxoSmithKline GmbH & Co.KG, Germany).

The composition of the bioequivalence batch is different than the proposed product, as uncoated tablets were used, while a coated formulation is applied for. Consequently, additional dissolution data is submitted to support the results obtained with the biobatch:

- The MAH demonstrated that the dissolution characteristics of the test and reference product as used in the bioequivalence study are similar in three different media. As a different composition is applied for than used in the bioequivalence study composition (uncoated→film-coated), the MAH has also shown that the dissolution characteristics are similar between bioequivalence test batch (uncoated tablets) and the proposed formulation (film-coated tablets) in three different media. Consequently, the dissolution profiles adequately support that the film-coated tablets have similar dissolution characteristics as the uncoated tablets used in the bioequivalence study. This is acceptable to support the results obtained in the bioequivalence study from a quality perspective.
- To support the biowaiver of strength, the MAH has demonstrated that the dissolution characteristics between the bioequivalence test batch (uncoated 500 mg tablets) and the 250 mg uncoated tablets are comparable. However, as the formulation has changed, the MAH has also demonstrated in three different media that the dissolution characteristics of the 250 mg uncoated tablets are comparable to the currently proposed formulation (250 mg film-coated tablets). The provided dissolution data is adequate to support the biowaiver of strength for the 250 mg film-coated tablets.

Overall the change in composition (uncoated→film-coated) can be considered as a minor change with no expected impact on the bioavailability.

### Biowaiver

Based on the dose proportional formulation, same manufacturing process, similar dissolution profile between the strengths and the linear pharmacokinetics, a biowaiver from the requirement to conduct the bioequivalence study for the lower strengths of 250 mg is granted.

### Bioequivalence study

#### *Design*

An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative bioequivalence study was carried out under fed conditions in 26 healthy male subjects, aged 18-36 years. Each subject received single dose (500 mg) of one of the two cefuroxime formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours 30 minutes after the start of intake of a high-fat high-calorie standard breakfast. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14 and 16 after administration of the products.

The design of the study is acceptable. The procedures followed for a fed study are according to the bioequivalence guideline. The sampling times are sufficient to provide a reliable estimate of the extent of exposure. A washout period of 11 days is considered appropriate. The handling and processing of the plasma samples are according to standard procedures.

*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*

Two subjects did not turn up at the second period and were dropped out of the study. Therefore, 24 subjects were eligible for pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> (median, range)) of cefuroxime under fed conditions.**

Treatment N=24	AUC <sub>0-t</sub> (ng.h/ml)	AUC <sub>0-∞</sub> (ng.h/ml)	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (h)
<b>Test</b>	30.96 ± 7.79	31.32 ± 7.79	7.61 ± 2.13	2.5 (2.0 - 5.0)
<b>Reference</b>	32.38 ± 7.46	32.68 ± 7.42	8.63 ± 2.46	2.75 (2.0 - 5.0)
<b>*Ratio (90% CI)</b>	0.95 (0.91 - 1.00)	--	0.89 (0.82 - 0.96)	--
<b>CV (%)</b>	11.14	--	20.09	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>CV</b> 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 Cefuroxim Mylan is considered bioequivalent with Zinnat.

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 Cefuroxim Mylan.

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

Important identified risks	<ul style="list-style-type: none"> <li>• History of hypersensitivity to cephalosporin antibiotic or severe hypersensitivity (anaphylactic reaction) to another beta-lactam agent (penicillins, monobactam or carbapenem)</li> <li>• Antibiotic associated colitis</li> <li>• Severe skin reaction such as Steven-Johnson syndrome and toxic dermal necrolysis</li> <li>• Severe haematological reactions (leucopenia, thrombocytopenia and haemolytic anaemia)</li> <li>• Nephrotoxicity with concomitant use with potent diuretics, aminoglycosides or amphotericin</li> <li>• Overgrowth of non-susceptible micro-organisms</li> <li>• Interference with diagnostic tests</li> <li>• Jarisch Herxheimer reaction</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Exposure during pregnancy and breastfeeding</li> <li>• Use in renal impairment</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in hepatic impairment</li> <li>• Effect on fertility</li> </ul>

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 (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 with two participants, followed by two rounds with ten 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 PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cefuroxim Mylan 250 mg and 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 June 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