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Public Assessment Report

Name of the Product:

Furocef

250 mg, 500 mg film-coated tablets

(cefuroxime)

Procedure number: HU/H/0387/001-002/DC

Marketing authorisation holder: Krka d.d.

Date: 5 August 2015

CONTENT

LAY SUMMARY

After careful assessment of their quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Furocef (Cefuroxim Krka in Austria, Ceftoren in Bulgaria, Ricefen in the Czech Republic and Lithuania) 250 mg and 500 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d.

The active substance is cefuroxime. Each film-coated tablet contains 250 mg or 500 mg cefuroxime, equivalent to 300.715 mg 601.43 mg or cefuroxime axetil, respectively.

The other ingredients are:

- tablet core: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal anhydrous silica, calcium stearate, calcium carbonate and crospovidone (type A);
- film coating: hypromellose (6 cp), titanium dioxide (E171), propylene glycol and brilliant blue FCF (E133).

The 250 mg film-coated tablets are blue color capsule shaped, biconvex ones with “204” debossed on one side and plain on the other side. Their dimensions are 15.1 mm x 8.1 mm.

The 500 mg film-coated tablets are blue color capsule shaped, biconvex ones with “203” debossed on one side and plain on the other side. Their dimensions are 19.1 mm x 9.1 mm.

The products are available in boxes containing the film-coated tablets in blisters.

Cefuroxime is an antibiotic used in adults and children above 40 kg. It works by killing bacteria that cause infections. It belongs to a group of medicines called *cephalosporins*.

Furocef is used to treat infections of:

- the throat,
- sinus,
- middle ear,
- the lungs or chest,
- the urinary tract,
- the skin and soft tissues.

Furocef can also be used to treat Lyme disease (an infection spread by parasites called ticks).

What patients need to know before taking Furocef?

Patients must not take Furocef if they

- are allergic to any cephalosporin antibiotics or any of the other ingredients of this medicine,
- have ever had a severe allergic (hypersensitive) reaction to any other type of betalactam antibiotic (penicillins, monobactams and carbapenems).

Warnings and precautions

Patients must look out for certain symptoms, such as allergic reactions, fungal infections (such as candida) and severe diahorrea (pseudomembranous colitis) while taking Furocef. This will reduce the risk of any problems.

If the patient needs a blood test

Furocef can affect the results of a test for blood sugar levels, or a blood screen called the Coombs test. If the patient needs a blood test, they should tell the person taking the sample that they are taking Furocef.

Other medicines and Furocef

Patients who are taking, have recently taken or might take any other medicines, if they have started taking any recently or start taking new ones should inform their doctor. This includes medicines that can be obtained without a prescription.

It is particularly important in case of probenecid and oral anticoagulants.

Medicines used to reduce the amount of acid in the stomach (e.g. antacids used to treat heartburn) can affect how Furocef works.

Furocef may reduce the effectiveness of the contraceptive pills. If the patient is taking the contraceptive pill while being treated with Furocef, she also needs to use a barrier method of contraception (such as condoms).

Furocef with food and drink

Patient should take Furocef after food. This will help to make the treatment more effective.

Pregnancy, breast-feeding and fertility

Patient s who are pregnant, think they might be pregnant or are planning to become pregnant, or who are breastfeeding, should inform their doctor. The doctor will consider the benefit of treating the patient with Furocefagainst the risk to the baby.

Driving and using machines

Furocef can make the patient dizzy and have other side effects that make him/her less alert. Patients should not drive or use machines if they do not feel well.

How to takeFurocef?

Furocef tablets should be taken after food. This will help to make the treatment more effec-

tive. It should be swallowed with some water. The tablets should not be chewed, crushed or split: this might make the treatment less effective.

The usual dose

For adults, the usual dose of Furocefis 250 mg to 500 mg twice daily depending on the severity and type of infection.

Use in children

Furocef250 mg and 500 mg film-coated tablets are not suitable for the treatment of small children under 40 kg.
Otherwise, its usual dose is 10 mg/kg (to a maximum of 125 mg) to 15 mg/kg (to a maximum of 250 mg) twice daily depending on the severity and type of infection.

Depending on the illness or how the adult patient or the child responds to treatment, the initial dose may be changed or more than one course of treatment may be needed.

Patients with kidney problems may need different doses, as prescribed by the doctor.

What to do if more Furoceftablets were taken then prescribed?

The patient may have neurological disorders, in particular they may be more likely to have fits *(seizures*)**.** They should contact their doctor or the nearest emergency hospital ward without a delay, showing the Furocefpack if possible.

What to do if taking Furocef tablets was forgotten?

Patients must not take a double dose to make up for a forgotten dose. They should just take their next dose at the usual time.

May taking Furocef tablets be stopped?

Patients should not stop taking Furocefwithout the doctor's advice. It is important taking the full course ofFurocef. It should not be stopped unless the doctor advises it – even if feeling better. If the full course of treatment is not completed, the infection may come back.

Possible side effects

Like all medicines, Furocefcan cause side effects, although not everybody experiences them.

Conditions the patients need to look out for

A small number of people taking Furocefgets allergic reactions or potentially serious skin reactions. Symptoms of these reactions include:
- severe allergic reaction. Their signs include raised and itchy rash, swelling, sometimes

of the face or mouth causing difficulty in breathing;
- skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler area, with a dark ring around the edge);
- a widespread rash with blisters and peeling skin. (These may be signs of *Stevens-Johnson syndrome* or *toxic epidermal necrolysis*);
- fungal infections. Medicines like Furocept can cause an overgrowth of yeast (*Candida*) in the body which can lead to fungal infections (such as thrush). This side effect is more likely if patients take Furocept for a long time;
- severe diarrhoea (*Pseudomembranous colitis*). Medicines like Furocept can cause inflammation of the colon (large intestine), causing severe diarrhoea, usually with blood and mucus, stomach pain, fever;
- Jarisch-Herxheimer reaction. Some patients may get a high temperature (fever), chills, headache, muscle pain and skin rash while being treated with Furocept for Lyme disease. This is known as the *Jarisch-Herxheimer reaction.* Symptoms usually last a few hours or up to one day.

Patients must contact a doctor or nurse immediately if getting any of these symptoms.

Common side effects (these may affect up to 1 in 10 people):
- fungal infections (such as *Candida*),
- headache,
- dizziness,
- diarrhoea,
- feeling sick,
- stomach pain.

Common side effects that may show up in blood tests:
- an increase in a type of white blood cell (*eosinophilia*),
- an increase in liver enzymes.

Uncommon side effects (these may affect up to 1 in 100 people):
- being sick,
- skin rashes.

Uncommon side effects that may show up in blood tests:
- a decrease in the number of blood platelets (cells that help blood to clot),
- a decrease in the number of white blood cells,
- positive Coomb's test.

Other side effects that have occurred in a very small number of people, but their exact frequency is unknown:
- severe diarrhoea (*pseudomembranous colitis*),
- allergic reactions,
- skin reactions (including severe ones),
- high temperature (*fever*),
- yellowing of the whites of the eyes or skin,
- inflammation of the liver (*hepatitis*).

Side effects that may show up in blood tests is that red blood cells destroyed too quickly (*haemolytic anaemia*).

How to store Furocef?

This medicinal product does not require any special storage conditions but keep it out of the sight and reach of children.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Austria, Bulgaria, Croatia, the Czech Republic, Estonia, France, Latvia, Lithuania, Poland, Portugal, Romania, the Slovak Republic, Slovenia and Spain) concerned the generic version of cefuroxime 250 mg and 500 mg film-coated tablets (Furocef, named Cefuroxim Krka in Austria Spain and France, and Ricefan in the Czech Republic, Latvia, Romania, Slovenia and Lithuania).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. In addition, the applicant has demonstrated bioequivalence between the submitted and the reference products.

The originator (and reference) products have been Zinnat® 250 mg, 500 mg film-coated tablets by GlaxoSmithKline Ltd. approved for more than 10 years.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Furocef 250 mg, 500 mg film-coated tablets containing cefuroxime (as cefuroxime-axetil), Krka d.d. Novo Mesto, Slovenia.

The products are indicated for the treatment of the infections listed below in adults and children above 40 kg:

- 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.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

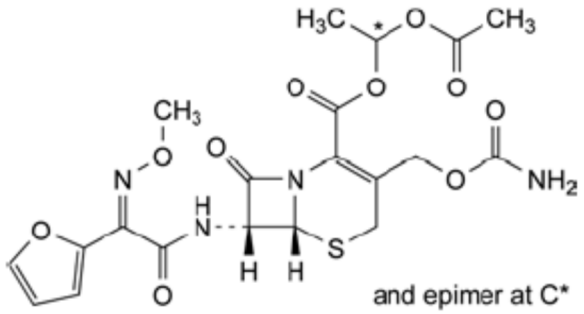
The chemical-pharmaceutical assessment report concerns the application of Furocef 250 mg and 500 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (generic application).

The reference product was Zinnat 500 mg tablet (GlaxoSmithKline) containing 500 mg cefuroxime as active ingredient.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using two European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: cefuroxime axetil
Chemical name: (1*RS*)-1-(acetyloxy)ethyl(6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate
Structure:



The active substance is white or almost white, crystalline powder, soluble in acetone, in ethyl acetate and in methanol, slightly soluble in ethanol (96 percent), insoluble in water. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph with additional requirements for residual solvents, bulk density and particle size.

The Ph. Eur. specification includes the following tests for cefuroxime axetil: appearance, solubility, identification (IR, HPLC), related substances, diastereoisomer ratio, crystallinity, acetone, water and assay.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated.

Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance as one CEP does not contain retest period. According to the presented stability data the proposed re-test period is acceptable in double low-density polyethylene (LDPE) bags and further placed in a well closed HDPE container with 25°C as storage condition.

The retest period and the packaging material (double polyethylene bags placed in a polyethylene drum) has been mentioned on the other CEP.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop immediate release tablets for oral administration containing cefuroxime as drug substance in 250 and 500 mg doses, which are pharmaceutically equivalent and bioequivalent to the reference medicinal product

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the products have been shown to be similar to the reference products.

A waiver for the smaller strengths is claimed, which is acceptable as all prescribed requirements are met.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies products with the following appearance were obtained:

- 250 mg strength: blue colour capsule shaped biconvex film-coated tablets with “204” debossed on one side and plain on the other side, dimensions 15.1 mm x 8.1 mm;
- 500 mg strength: blue colour capsule shaped biconvex film-coated tablets with “203” debossed on one side and plain on the other side, dimensions 19.1 mm x 9.1 mm.

The excipients used in the finished product are microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal anhydrous silica, calcium stearate, calcium carbonate and crospovidone (type A). The film-coating [RB1]contains hypromellose (6cp), titanium dioxide (E171), propylene glycol and FD &C blue no. 1 aluminium lake.

All excipients used, except [RB2]film-coating agent complies with their respective Ph. Eur. monograph.

Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister packs. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is approved.
The SmPC, the Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The application was based on demonstrating bioequivalence to marketed reference products.

The pharmaco-toxicological properties of cefuroxime are well-known. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to cefuroxime.

III.2 Pharmacology

The active substance cefuroxime axetil is a prodrug of the second generation cephalosporin cefuroxime. Cephalosporins work the same way as penicillins: they interfere with the peptidoglycan synthesis of the bacterial wall by inhibiting the final transpeptidation needed for the cross-links. This effect is bactericidal. Cefuroxime is effective against the following organisms: Aerobic Gram-positive microorganisms: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*. Aerobic Gram-negative microorganisms: *Escherichia coli*, *Haemophilus influenzae* (including beta-lactamase-producing strains), *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis* (including beta-lactamase-producing strains), *Neisseria gonorrhoeae* (including beta-lactamase-producing strains). Spirochetes: *Borrelia burgdorferi*.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the body to release cefuroxime into the circulation.

III.4 Toxicology

No toxicity studies were submitted by the Applicant.

Published information on toxicological studies with cefuroxime axetil was the basis for the evaluation. Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the in-

terference in clinical laboratory tests in humans.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Furocef 250 mg and 500 mg film coated tablets are 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of cefuroxime axetil are well-known. As Furocef is a generic product there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant has not conducted any clinical studies with Furocef and all the relevant clinical information provided in the Clinical overview is literature based.

To support the application the applicant has submitted a report of one bioequivalence study comparing Furocef (cefuroxime) film-coated tablet 500 mg (Test product, T) with Zinnat® (cefuroxime) film-coated tablet 500 mg (marketed by GlaxoSmithKline Ltd., Reference product, R) in healthy male human subjects under fed condition.

IV.2 Pharmacokinetics

IV.2.1 Literature data

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the body to release cefuroxime into the circulation. Approximately 60% of an administered dose is absorbed. Optimum absorption occurs when it is administered after a light meal.

The mean peak serum level of cefuroxime following a 250 mg dose in normal healthy adults, after food, was 4.1 mg/L and occurred two to three hours after dosing. Unhydrolysed drug has not been detected in the serum but 1-2% of the administered dose is excreted in the urine in a form which indicates that small amounts of the intact ester are absorbed into circulation. There were linear relationships between dose and both maximum serum cefuroxime concentration and area under the serum drug concentration-versus-time curve. The mean half-life of cefuroxime in serum was independent of dose and ranged from 1.4 to 1.9 h. Protein binding has been variously stated as 33-50% depending on the methodology used. Cefuroxime is not metabolised to any significant extent.

Excretion occurs mainly through the kidney both by glomerular filtration and tubular secretion.

IV.2.2 Bioequivalence study

The main objective of this study was to prove bioequivalence between Cefuroxime 500 mg film-coated tablets [M3] and Zinnat® 500 mg film-coated tablets (GlaxoSmithKline Ltd.) (Reference product - R) in healthy adult males, under fed conditions and to monitor safety of subjects included in the study.

Biowaiver

The applicant claimed for biowaiver for the 250 mg dose strength on the basis of generalbiowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) Both the strength i.e. 250 mg and 500 mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) The qualitative composition of Ceftoren 250 mg film-coated tablets is same as that of Ceftoren 500 mg film-coated tablets.
c) The composition of the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for both strengths.
d) The in-vitro dissolution profile is similar under identical conditions for the additional strength i.e. 250mg and the strength of the batch used in the bioequivalence study i.e. 500mg.
e) Cefuroxime exhibits linear pharmacokinetics in the therapeutic range of 125-500 mg.

Biowaiver claim for the 250 mg dose strength is acceptable according to general requirements for biowaiver (CPMP/EWP/QWP/1401/98, Rev. 1/ Corr **).

The study

The design of this investigation was a randomized, open label, laboratory blind, cross over, two-period, two treatment, two sequence, single dose, bioequivalence study study in healthy male subjects under fed condition.

Blood samples were collected in pre-labelled sodium heparin blood sample collection vacuum tubes during each period.

The plasma samples of subjects were analysed using validated LC-MS/MS method for Cefuroxime.

The pharmacokinetic parameters determined were as follows:

- primary: AUC_{0-t}, $AUC_{0-\infty}$, C_{max},
- other: T_{max}, $t_{1/2}$, K_{el}.

The statistical methods used in evaluation were:

- descriptive statistics of PK parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test (T) and reference (R) pharmacokinetic data,
- log-transformation of $AUC_{0-\infty}$, AUC_{0-t} and C_{max} data,
- evaluation of data using a linear mixed-effects model (SAS® 9.1.3 or higher, SAS Inst. Inc., USA), with the main effects of treatment, period and sequence and subjects nested within sequence in ANOVA, - calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters,

- applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon signed rank test).

The applicant stated that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

The summary of the results of the study can be seen on the next Table.

Pharmacokinetic parameter	Ratio T/R	90% Confidence intervals	
		Lower 90% CI	Upper 90% CI
AUC_{0-t}	99.01	97,00	101,07
C_{max}	103,34	99,94	106,86

Results derived from the analysis of log-transformed primary efficacy parameters of C_{max}, AUC $_{0-t}$ and AUC 0-∞ for cefuroxime, the T/R ratios of LS mean values of the two groups and their 90% confidence intervals also were included within the acceptance range of 80% - 125%. Thus, results support the bioequivalence between the test and reference products.

Conclusion on the bioequivalence study

Based on the submitted bioequivalence study the Furocef 500 mg film-coated tablet are considered bioequivalent with the Zinnat® (Cefuroxime) 500 mg film-coated tablet, (Glaxo SmithKline Ltd.). The results obtained in this study for the 500 mg strength could be extrapolated to the other claimed 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.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

Cefuroxime is a β-lactam type antibiotic, a second-generation cephalosporin. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that cefuroxime interferes with an autolysin inhibitor.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of cefuroxime.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application.

No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• History of hypersensitivity to cephalosporin antibiotic or severe hypersensitivity (anaphylactic reaction) to another beta-lactam agent (penicillins, monobactam or carbapenem) • Antibiotic associated colitis • Severe skin reactions such as Stevens-Johnson syndrome and toxic dermal necrolysis
Important potential risks	• Use during breastfeeding • Use in renal impairment
Missing information	Not applicable

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Krka's product of cefuroxime axetil 250 mg and 500 mg film-coated tablets. No additional activities are proposed.

Risk minimisation measures: routine measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected Krka's product of cefuroxime axetil 250 mg and 500 mg film-coated tablets. No additional activities are proposed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The active substance cefuroxime axetil is listed on the EURD list (EMA/630645/2012 Rev. 31 Corr – 30/06/2015); with a submission frequency of five years and a Data Lock Point of 07/04/2017.

Currently, no routine PSUR reporting is required for generic products containing cefuroxime axetil.

IV.7 Discussion on the clinical aspects

The application concerns a generic version of cefuroxime axetil.

Abridged applications avoid the need for repetitive tests on animals and humans. For these applications the bioequivalence study described in section IV.2.2 are pivotal.

To support the application the applicant has adequately demonstrated bioequivalence between Furocef film-coated tablets and the reference product Zinnat 250 mg, 500 mg film-coated tablets.

There is no objection against granting the marketing authorization from clinical points of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concerns Furocef 250 mg and 500 mg film-coated tablets, generic versions of cefuroxime (as cefuroxime axetil). The applicant and the future holder of authorisation is Krka d.d., Slovenia.

The indication is treatment of adult patients and children above 40 kg with

- 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.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Zinnat® mg film-coated tablets (GlaxoSmithKline Ltd.) The bioequivalence was adequately proven.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Furocef 250 mg and 500 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 language used for the purpose of user testing the patient information leaflet was Hungarian.

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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached