CBG MEB

Public Assessment Report

Scientific discussion

Amoxicilline Eurogenerics 500 mg/5 ml, powder for oral suspension

(amoxicillin trihydrate)

NL/H/3412/001/DC

Date: 17 January 2017

This module reflects the scientific discussion for the approval of Amoxicilline Eurogenerics 500 mg/5 ml, powder for oral suspension. The procedure was finalised on 3 June 2016. 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
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 Amoxicilline Eurogenerics 500 mg/5 ml, powder for oral suspension from Eurogenerics NV.

Amoxicilline Eurogenerics is indicated for the oral treatment of the following infections in adults and children (see SmPC sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbation of chronic bronchitis
- Community-acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- *Helicobacter pylori* eradication
- Lyme disease

Amoxicilline Eurogenerics is also indicated for the prophylaxis of endocarditis.

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 Clamoxyl 500 mg/5 ml powder for oral suspension by Laboratoire GlaxoSmithKine, which was first registered in France in 1983.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Amoxicilline Eurogenerics is a white to yellowish powder for preparing a homogenous suspension with fruity aromatic odour.

The powder for oral suspension is packed in an brown glass bottle, closed by a HDPE white screw cap with tamper evident ring. The bottles are packed together with a dosing device; either a 6 ml PE syringe (with CE marking), a 5 ml PE spoon (with CE marking) or a 5 ml cup (with CE marking).

To obtain the reconstituted suspension, water should be added to the powder in the bottle. When reconstituted, every 5 ml of oral suspension contains amoxicillin trihydrate equivalent to 500 mg amoxicillin. Different volumes are available.

The excipients are crospovidone type A, silicon dioxide, xanthan gum, colloidal anhydrous silica, acesulfame potassium, saccharin sodium and strawberry flavour (maltodextrin, modified starch (E1450), natural flavouring substances and flavouring preparations).

II.2 Drug Substance

The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white crystalline powder. It is slightly soluble in water, slightly soluble in ethanol, practically insoluble in fatty oils. Amoxicillin trihydrate does not show polymorphism or isomerism.

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 specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 6 years 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. Except for the strawberry flavour, the used excipients are all well known, pharmacopoeial substances, usual for the type of product, powder for oral suspension. All excipients are considered to be safe in the proposed concentrations. The container closure system is usual for this type of product.
The proposed strength is based on the dissolution performance of the corresponding strength of the innovator product. The MAH demonstrated by in-use stability testing (with simulated openings three times a day) and with challenges tests with various micro-organisms, that the use of a preservative is not needed to keep the reconstituted suspension in adequate microbiological condition meeting the requirements set.

A bioequivalence study was submitted to demonstrate bioequivalence between Amoxicilline Eurogenerics powder and the reference medicinal product, Clamoxyl.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The commercial manufacturing process with the repeating sequence of weighing, blending, compacting, sieving, final blending, and filling into bottles, can be considered as a standard process. Process validation data on the product will be presented for 3 commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients except for the strawberry flavour are in accordance with the requirements of the corresponding Ph.Eur. monographs. Regarding the strawberry flavour the MAH made assumable that the mixture of all flavour components can be sufficiently identified.
However, the MAH committed to submit an identification method on the flavour as replacement of the current identification method. The commitment is considered acceptable.

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, average mass (uniformity of weight), identification, pH of suspension, water content, dispersability/suspendability, assay, degradation products, and microbiological purity. The absence of the tests for dissolution, particle size and rheological properties from the finished product specification has been discussed and fully justified by the MAH. Limits in the specification have also 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 2 batches of 500 mg/5 ml 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 24 months at long-term conditions and 6 months at accelerated conditions for 2 batches of 500 mg/5 ml. For the powder there is only a moderate increase of total impurities and moderate assay decreases. Also an out-of-spec was observed for amoxicillin assay. The photostability studies as performed are considered acceptable, and the conclusion that there is no impact on quality of the tested powder for oral suspension products when exposed to light in its immediate packaging, is endorsed. In view of this the granted shelf-life is 24 months when stored not above 25°C in amber glass bottles with HDPE screw cap.

The EMA guideline on in-use stability requires testing of at least two pilot-scale batches. Both in-use stability batches have been stored for 25 months at 25°C/60% RH. All results during testing at days 0-7-10 meet the requirements, and there is not a striking difference between the two strengths. Herewith the shelf-life of the reconstituted suspension is 10 days if stored in a refrigerator (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 Amoxicilline Eurogenerics powder for oral suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:
- The MAH commits to submit an identification method of the strawberry flavour, as replacement of the current identification method.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amoxicilline Eurogenerics powder for oral suspension 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 Clamoxyl 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

Amoxicilline trihydrate 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 one bioequivalence study in which the pharmacokinetic profile of the test product Amoxicilline Eurogenerics (Eurogenerics N.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Clamoxyl powder for oral suspension (GlaxoSmithKline, France):

- Study I - A bioequivalence study under fasting conditions with the 500 mg/5 ml strength

The choice of the French reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical and dose proportional to the formula proposed for marketing.

Bioequivalence study

Design
A randomised, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 21-42 years. Each subject received a single dose (500 mg/5 ml amoxicillin oral suspension) of one of the 2 amoxicillin formulations. 5 ml of suspension was administered with a syringe. The syringe was rinsed with a part of 240 ml water and the rinsing solution was administered too. This procedure was repeated 3 times. Thereafter, the remaining volume of water was administered. The suspensions were administered after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. There is not food interaction for amoxicillin and the suspension can be taken with or without food.

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
One subject withdrew for personal reason and one subject was withdrawn due to adverse events. Therefore 24 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin 500 mg/5 ml suspension under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h

Test	35014 ± 6355	35357 ± 6329	11810 ± 2588	1.50 (1.0 – 2.5)	1.4 ± 0.2
Reference	37270 ± 7188	37571 ± 7233	12626 ± 2505	1.38 (1.0 – 2.5)	1.3 ± 0.2
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	--	0.93 (0.87 – 0.99)	--	--
CV (%)	7.23	--	13.06	--	--

$AUC_{0-\infty}$ 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 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 stud Amoxicilline Eurogenerics powder for oral suspension is considered bioequivalent with Clamoxyl powder for oral suspension.

The MEB has been assured that the bioequivalence studies have 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 Amoxicilline Eurogenerics.

Summary table of safety concerns as approved in RMP:

Important identified risks	- Hypersensitivity - Hepatic events (hepatitis, cholestatic jaundice, rises in AST/ALT)
Important potential risks	- Acute generalised exanthemous pustulosis - Antibiotic associated colitis - Lack of efficacy due to resistance - Reduced efficacy of oral hormonal contraceptives
Missing information	- Exposure during pregnancy - Exposure through human milk

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 Clamoxyl powder for oral suspension. 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

For the reference product Clamoxyl/Amoxil, an Article 30 referral procedure has been finalised. The product information of Amoxicilline Eurogenerics is fully aligned with the outcome of this referral. Therefore the absence of a user test regarding the content of the leaflet is acceptable. A bridging report for the layout has been submitted. The results have been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline Eurogenerics 500 mg/5 ml powder for oral suspension has a proven chemical-pharmaceutical quality and are generic forms of Clamoxyl 500 mg/5 ml powder for oral suspension. Clamoxyl 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 Amoxicilline Eurogenerics with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 June 2016.

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
The composition of the flavour has changed because of replacement of supplier for the excipient Strawberry flavour. The manufacturer has developed a new method of analysis to identify the strawberry flavour to replace the approved method Editorial change in the product information (device cup volume)	NL/H/3412/IB/001/G	IB	22-8-2016	5-11-2016	Approval	No
Minor change in the manufacturing process	NL/H/3412/001/IA/002	IA	18-11-2016	18-12-2016	Approval	No
Device with CE marking	NL/H/3412/001/IA/003	IA	7-12-2016	6-12-2016	Approval	No