COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amoxicilline EG 1000 mg, tablets (amoxicillin trihydrate)

NL/H/5103/001/DC

Date: 8 February 2022

This module reflects the scientific discussion for the approval of Amoxicilline EG 1000 mg, tablets. The procedure was finalised on 23 June 2021. 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
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 EG 1000 mg, tablets, from Eurogenerics N.V.

The product is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations 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 EG is also indicated for the prophylaxis of endocarditis.

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 1g dispersible tablets which has been registered by Laboratoire GlaxoSmithKline in France since 23 February 1988. In the Netherlands, Clamoxyl had been registered since 1979 (NL RVG 08298), but was withdrawn in 2005.

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 EG are white or off/white oblong shaped tablets with one score-line on both sides. The tablets can be divided into equal doses and contain as active substance 1000 mg of amoxicillin (as amoxicillin trihydrate).

The tablets are packed in blisters of PVC/PVDC/Aluminium or PVC/TE/PVDC/Aluminium.

The excipients are: magnesium stearate (E470b), cellulose microcrystalline (E460), crospovidone (E1202), aspartame (E951) and strawberry flavour (contains: maize maltodextrin, triethyl citrate (E1505), flavouring components, propylene glycol (E1520) and benzylalcohol)

II.2 Drug Substance

The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is slightly soluble in water. Amoxicillin trihydrate has four chiral centres and is the 2S,5R,6R,2'R-isomer. Polymorphs of amoxicillin trihydrate have not been described in literature.

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. with additional tests for, tapped bulk density, and microbiological quality. The specification is 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 three full scale batches.

Stability of drug substance

The active substance is stable for six years when stored in a polyethylene bag in a sealed laminate bag placed in a carton box. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is discussed and their functions explained. Product development trials were carried out with the aim of producing a stable, oral formulation, possessing satisfactory physicochemical properties that are comparable with the reference drug product attributes in compliance with oral drug products. During development, design of experiments was applied to achieve the final formulation, but no design space or proven acceptable ranges are claimed or granted. Comparative *in vitro* dissolution data for the 1000 mg test and reference product used in the bioequivalence studies have been provided. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process concerns a standard process which involves the blending of the drug substance to a basic blend and final blend, tableting and finally packaging. The manufacturing process has been validated and process validation data on the product have been presented for eight batches, in accordance with the relevant guidelines. The validation data is considered sufficient, especially as further validation will be performed post authorisation.

Control of excipients

The excipients used and their quantities applied are common for solid oral dosage forms. All excipients are in line with their Ph. Eur. monograph or in-house specification. 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, dimensions, mass and uniformity of dosage units, identification, assay, degradation products, dissolution, disintegration time, hardness, water content and microbiological purity. The release and end-of shelf-life specifications are identical with the exception of the limit for total impurities. 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 on six batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the drug product have been provided for batches stored at 25°C/60%RH (48 months), 30°C/65%RH (12 months), and 40°C/75%RH (six months) in accordance with applicable ICH guidelines. From the available stability data an increase in impurities and a decrease in assay and dissolution have been noted, however, all staying within specification under long term conditions, up to 36 months. Under accelerated and long term conditions some batches showed out-of-specification results at the end of the tested period.

On basis of the data submitted, a shelf life was granted of 36 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The labelled storage conditions "Do not store above 25°C. Store in the original package in order to protect from moisture." are considered acceptable.

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 EG 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 Amoxicilline EG 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 1g dispersible tablets 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

Amoxicillin 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 a bioequivalence study in which the pharmacokinetic profile of the test product Amoxicilline EG 1000 mg, tablets (DSM Sinochem Pharmaceuticals Netherlands B.V.) is compared with the pharmacokinetic profile of the reference Clamoxyl 1g dispersible tablets (GlaxoSmithKline B.V., France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test and reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, balanced, open-label, two-period, two-sequence, two-way crossover oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 23-44 years. Each subject received a single dose (1000 mg) of one of the two amoxicillin trihydrate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.50, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable.

Amoxicillin trihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of amoxicillin trihydrate. Therefore,

a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with *The Guideline on the Investigation of Bioequivalence*.

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 was replaced by a standby subject before dosing, as a subject was not willing to continue to participate in the study. One subject did not report to facility for Period II check in. 27 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=27	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	48125 ± 9671	48619 ± 9875	14010 ± 3667	2.0 (0.83 – 5.5)	1.6 ± 0.3
Reference	49011 ± 11332	49543 ± 11652	15424 ± 4871	2.5 (1.67 – 5.0)	1.6 ± 0.3
***Ratio (90% CI)**	0.99 (0.93 – 1.05)	-	0.98 (0.91 – 1.06)	-	-
CV (%)	14.1	-	16.1	-	-

$AUC_{0-\infty}$ 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 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 Amoxicilline EG is considered bioequivalent with Clamoxyl.

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 Amoxicilline EG.

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

Important identified risks	• Hypersensitivity reactions (anaphylactoid) • Convulsions • Acute generalized exanthemous pustulosis (AGEP) • Hepatic events • Antibiotic associated colitis
Important potential risks	• Prolongation of prothrombin time due to concomitant use with oral anticoagulants
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 1g dispersible tablets. 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 language used for the purpose of user testing the PL was English. 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline EG 1000 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Clamoxyl 1g dispersible tablets. 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 EG with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 June 2021.

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