CBG MEB

Public Assessment Report

Scientific discussion

Amoxicilline DSM Sinochem 500 mg, 750 mg and 1000 mg dispersible tablets

(amoxicillin trihydrate)

NL/H/3341/001-003/DC

Date: 5 September 2016

This module reflects the scientific discussion for the approval of Amoxicilline DSM Sinochem 500 mg, 750 mg and 1000 mg dispersible tablets. The procedure was finalised on 18 November 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
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 Amoxicilline DSM Sinochem 500 mg, 750 mg and 1000 mg dispersible tablets, from DSM Sinochem Pharmaceuticals Netherlands B.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

Amoxicillin 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 that is registered in France under the name Clamoxyl 1 g, dispersible tablets since 23 February 1988 by Laboratoire GlaxoSmithKline. In the Netherlands reference is made to a historical reference product: the innovator product Clamoxyl DuoDispers 750 mg and 1000 mg, tablets which was authorised by GlaxoSmithKline B.V. respectively in 1975 and 1979 (NL license RVG 6700 and 8298). These products have been withdrawn for commercial reasons on 31 December 2005. The Dutch product was part of the same global marketing authorisation as the Spanish product.

The concerned member state (CMS) involved in this procedure was Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Amoxicilline DSM Sinochem is a white or off-white oblong shaped tablet with one score-line on both sides. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Each dispersible tablet contains 500 mg, 750 mg or 1000 mg amoxicillin, as 574 mg, 861 mg or 1148 mg amoxicillin trihydrate.

The tablet is packed in a PVC/PVDC/Aluminium blister.

The excipients are: magnesium stearate (E470b), microcrystalline cellulose (E460), crospovidone (E1202), aspartame (E951), and strawberry flavour.

Components of the strawberry flavour: maize maltodextrin, tri-ethyl citrate (E1505), flavouring components, propylene glycol and benzyl alcohol.

The tablet strengths are dose proportional.

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 three 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. The choice of excipients is discussed and their functions explained. The pharmaceutical development of the product has been adequately performed.

One bioequivalence study has been performed to demonstrate bioequivalence between Amoxicilline DSM Sinochem 1000 mg dispersible tablets and Clamoxyl 1000 mg dispersible tablets. The reference batch from France is acceptable. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Comparative *in vitro* dissolution data for the 1000 mg test and reference product used in the bioequivalence study as well as between the additional test strengths (500 mg and 750 mg) are provided at pH 1.2, 4.5 and 6.8. The provided dissolution profiles are sufficient to conclude the *in vitro* similarity between the test and the reference products.

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 process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two full scale batches in accordance with the relevant European guidelines.

Control of excipients
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, fineness of dispersion, and microbiological purity. 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 two batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the drug product has been provided on two full scaled batches per strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Aluminium blisters. From the available stability data an increase in impurities and a decrease in assay and dissolution have been noted. However the product remains well within the specification throughout the proposed shelf-life.
Based on the provided stability data a shelf life of 18 months can be granted. The product has the following storage conditions: “Do not store above 25°C” and “Store in the original package in order to protect from moisture”. A photostability study in line with ICH guidelines has been performed showing that both directly exposed drug product tablets and tablets exposed in its primary packing are photostable.

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 DSM Sinochem 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 DSM Sinochem 500 mg, 750 mg and 1000 mg dispersible 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.2 Discussion on the non-clinical aspects

These products are generic formulations of Clamoxyl 500 mg, 750 mg and 1000 mg dispersible tablets which are 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

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

The choice of the reference product
The choice of the French 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. The batch size of the biobatch is acceptable.

Biowaiver
The MAH has carried out a bioequivalence study on the highest strength (1000 mg). The results of this study can be extrapolated to the lower strengths, as the criteria for biowaiving additional strengths have been fulfilled:

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

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover 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 2 amoxicillin 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 7 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.

A single dose, crossover study under fasting conditions was carried out. This is acceptable, as there is no food interaction for amoxicillin and the tablets can be taken with or without food. The design of the study is acceptable.

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 did not report for Period II. The remaining 27 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin 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	14524 ± 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	--	16.4	--	--

$AUC_{0-\infty}$	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 DSM Sinochem 1000 mg dispersible tablets is considered bioequivalent with Clamoxyl 1000 mg dispersible tablets.

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 DSM Sinochem dispersible tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity
Important potential risks	• Acute generalised exanthemous pustulosis (AGEP) • Antibiotic-associated colitis • Convulsions in renal impaired patients • Prolongation of prothrombin time and bleeding time • 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 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 test consisted of a pilot test with two participants, followed by two rounds with 10 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

Amoxicilline DSM Sinochem dispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Clamoxyl 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 DSM Sinochem dispersible tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 November 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