CBG MEB

Public Assessment Report

Scientific discussion

Amoxicilline/Clavulaanzuur DSM Sinochem 875 mg/125 mg powder for oral suspension in sachet

(amoxicillin trihydrate and potassium clavulanate)

NL/H/3261/001/DC

Date: 26 July 2016

This module reflects the scientific discussion for the approval of Amoxicilline/Clavulaanzuur DSM Sinochem 875 mg/125 mg powder for oral suspension in sachet. The procedure was finalised on 7 October 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
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/Clavulaanzuur DSM Sinochem 875 mg/125 mg powder for oral suspension in sachet, 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 (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis

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 Augmentin 875 mg/125 mg powder for oral suspension in sachet, which has been registered in Spain by GlaxoSmithKline S.A. since 2 March 1993.
In the Netherlands Augmentin 875 mg/125 mg powder for oral suspension is not registered. Augmentin was however authorised as film-coated tablets in the same strength, 875 mg/125 mg (NL Licence RVG 18553); the strength is no longer registered.

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

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

II. QUALITY ASPECTS

II.1 Introduction

The product is an off white to yellowish powder for oral suspension.

The powder is packed in a polyethylene terephthalate/aluminium/polyethylene sachet.

Each sachet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

The excipients are: crospovidone (E1202), colloidal anhydrous silica (E551), aspartame (E951), magnesium stearate (E470b), strawberry flavour.

II.2 Drug Substances

The active substances are amoxicillin trihydrate and potassium clavulanate diluted with silicon dioxide in the ratio 1:1. Both are established active substances described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white crystalline powder which is slightly soluble in water. Potassium clavulanate is a white or almost white crystalline powder, which is freely soluble in water. No polymorphism or isomerism is described for either active substance.

The CEP procedure is used for both active substances. 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
CEPs has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances
The drug substance specifications are in line with the Ph.Eur and additional requirements are laid down on the CEPs. The specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches for amoxicillin trihydrate. For potassium clavulanate sufficient data have been provided.

Stability of drug substances
The active substance amoxicillin trihydrate is stable for 6 years when stored under the stated conditions. Potassium clavulanate is stable for 48 months at 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 used excipients are all well known pharmacopoeial substances. All excipients are considered to be safe in the proposed concentrations. Both proposed strengths are based on the appearance and dissolution performance of the corresponding strengths of the innovator product. The dispersion pattern/dispersability/suspendability of the powder in water was checked in the lowest and highest amount of water stated in the innovator SmPC, i.e. 10 ml and 20 ml. Both test and reference product dispersed within 2 minutes. The pharmaceutical development of the product has been adequately performed.

Two bioequivalence studies have been performed to demonstrate bioequivalence between Amoxicilline/Clavulaanzuur DSM Sinochem and Augmentin. The reference bio-batches from Spain is considered acceptable. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. The MAH provided comparative dissolution studies between the test- and reference bio-batches at pH 4.5 and 6.8 according to the guideline on the investigation of bioequivalence. The absence of pH 1.2 is justified because clavulanic acid degrades very rapidly in pH 1.2.

Manufacturing process
Detailed flow charts of the four stages for the manufacturing of the two strengths are provided. The process consists of manufacturing the basic blend, manufacturing the final blend, filling and sealing the sachets, and packaging. It is confirmed as a standard process. The applied in-process controls are considered adequate and the process validation protocols for manufacturing both strengths at the various scales are considered acceptable. Full process validation will be performed on three consecutive batches of the product for commercial batch size.

Control of excipients
All excipients meet the specifications of the respective Ph.Eur. monographs. 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, identification, uniformity of dosage units, HPLC assay, HPLC degradation products, water content, 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 three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Three batches of each strength have been stored in the proposed packaging for 24 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. All intermediate and long-term results meet the set requirements. In view of out-of-specification results observed at accelerated conditions, the storage condition “Not above 25°C” is justified. On the basis of the data submitted, a shelf-life of 24 months was granted. Also the product is to be stored in the original package in order to protect it from moisture.

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/Clavulaanzuur DSM Sinochem has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

Two post-approval commitments were made:

- The MAH committed to evaluate the total (shelf-life) limit for impurities at the end of the 36 months long-term stability study for the 875 mg/125 mg powder for suspension in sachet and to consider tightening of the current specification.
- In addition the MAH committed to evaluate the release and shelf-life limit on water content at the end of the 36 months long-term stability study for the 875 mg/125 mg powder for suspension in sachet and to consider tightening of the current specification.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amoxicilline/Clavulaanzuur DSM Sinochem 875 mg/125 mg powder for oral suspension in sachet 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

The product is a generic formulation of Augmentin 875 mg/125 mg powder for oral suspension 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 and potassium clavulanate are well-known active substances 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 initially submitted a bioequivalence study under fasting conditions. However, as stated in the SmPC of Augmentin, the dose should be administered at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid. As stated in the EMA guideline on the investigation of Bioequivalence, for products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions. Therefore the MAH submitted an additional bioequivalence study, conducted under fed conditions. The two studies are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Amoxicilline/Clavulaanzuur DSM Sinochem (DSM Sinochem Pharmaceuticals Netherlands B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Augmentin powder for oral suspension in sachet (GlaxoSmithKline S.A., Spain):

- Study I - A bioequivalence study under fasting conditions with the 875 mg/125 mg strength
- Study II - A bioequivalence study under fed conditions with the 875 mg/125 mg strength

The choice of the reference products in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I –Amoxicillin/Clavulaanzuur DSM Sinochem 875 mg/125 mg vs Augmentin under fasting conditions
Design
A single-dose, randomised, balanced, open-label, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-39 years. Each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the 2 formulations. After an overnight fast the content of the sachet was poured into a container with approximately 20 ml of water (at least 10 minutes prior to schedule dosing time and not more than 30 minutes from the scheduled dosing time) and stirred until the formation of suspension. The content was swirled to aid in dispersion and to form homogeneous solution before swallowing. Subjects were instructed to drink the whole suspension, and the container was rinsed for three times with 220 ml water. Fasting was continued for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 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.

Results
One subject did not report for Period II. 39 subjects completed the study and were included in the statistical analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 875 mg amoxicillin under fasted conditions.

Treatment N=39	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	47485 ± 9773	47946 ± 9932	13165 ± 3305	2.0 (0.83 – 3.5)	1.7 ± 0.3
Reference	47055 ± 11501	47452 ± 11607	13861 ± 4201	1.67 (1.0 – 4.5)	1.7 ± 0.4
***Ratio (90% CI)**	1.02 (0.96 – 1.08)	--	0.97 (0.90 – 1.03)	--	--
CV (%)	15.0	--	16.8	--	--

$AUC_{0-\infty}$ 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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 125 mg clavulanic acid under fasted conditions.

Treatment N=39	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	8130 ± 2435	8218 ± 2446	3620 ± 1261	1.0 (0.67 – 3.0)	1.2 ± 0.3
Reference	8434 ± 2539	8521 ± 2545	3668 ± 1262	1.0 (0.67 – 2.0)	1.2 ± 0.3
***Ratio (90% CI)**	0.97 (0.90 – 1.04)	--	0.98 (0.90 – 1.07)	--	--
CV (%)	18.9	--	22.9	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study II –Amoxicillin/Clavulaanzuur DSM Sinochem 875 mg/125 mg vs Augmentin under fed conditions

Design
A single-dose, randomised, balanced, open-label, two-treatment, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 21-39 years. Subjects were fasted overnight for at least 10 hours prior to the start of the breakfast. 30 minutes after the start of a high fat, high calorie, non-vegetarian breakfast each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the 2 formulations. The contents of the sachet was poured into a container with approximately 20 ml of water (at least 10 minutes prior to schedule dosing time and not more than 30 minutes from the scheduled dosing time) and stirred until the formation of suspension. The contents was swirled to aid in dispersion and to form homogeneous solution before swallowing. Subjects were instructed to drink the whole suspension,

and the container was rinsed for three times with the remaining water 220 ml (i.e. 240 - 20 = 220 ml). For each subject there were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 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. Instead of at the start of a meal, the formulation was administered 30 min after the start of intake of a meal. Although not fully in accordance with the SmPC, it is considered acceptable.

Results
Three subjects were withdrawn in Period I due to AEs. One subject did not report for Period II. 36 subjects completed the study and were included in the statistical analysis.

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 875 mg amoxicillin under fed conditions.

Treatment N=36	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	43937 ± 8833	44471 ± 9018	10595 ± 2449	2.0 (1.0 – 3.5)	1.6 ± 0.2
Reference	45214 ± 8909	45820 ± 9085	10815 ± 2179	2.0 (1.33 – 3.5)	1.7 ± 1.1
***Ratio (90% CI)**	0.97 (0.94 – 1.00)	--	0.97 (0.92 – 1.03)	--	--
CV (%)	7.9	--	14.7	--	--

$AUC_{0-\infty}$	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*

Table 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 125 mg clavulanic acid under fed conditions.

Treatment N=36	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	4332 ± 1634	4407 ± 1636	1634 ± 490	1.33 (0.5 – 3.0)	1.1 ± 0.1
Reference	4292 ± 1758	4388 ± 1747	1606 ± 537	1.5 (0.67 – 2.5)	1.1 ± 0.2
***Ratio (90% CI)**	1.02 (0.93 – 1.13)	--	1.02 (0.92 – 1.14)	--	--
CV (%)	24.6	--	27.2	--	--

$AUC_{0-\infty}$	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 studies

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 studies under fasted and fed conditions, the Amoxicilline/Clavulaanzuur DSM Sinochem 875 mg/125 mg powder for oral suspension is considered bioequivalent with the Augmentin 875 mg/125 mg 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/Clavulaanzuur DSM Sinochem powder for oral suspension.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity • Hepatic impairment
Important potential risks	• Acute generalised exanthemous pustulosis (AGEP) • Antibiotic-associated colitis • Increased risk of neonatal necrotizing enterocolitis (when amoxicillin/ clavulanic acid is used prophylactic in women with preterm, premature rupture of the foetal membrane) • Lack of efficacy due to resistance
Missing information	• Exposure during pregnancy • Exposure through human milk • Exposure in children under 2 years

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 Augmentin. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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 user tested PL for Amoxicilline/Clavulaanzuur DSM Sinochem film-coated tablets was found similar enough to the PL for Amoxicilline/Clavulaanzuur DSM Sinochem powder for oral suspension in sachet, that a combination of bridging and a focus test would suffice in demonstrating the readability for the leaflet for Amoxicilline/Clavulaanzuur DSM Sinochem powder for oral suspension in sachet.

As such, a focus test was conducted to address the aspects of the powder for oral suspension in sachet PL which were not addressed in the bridging report. The user testing has been adequately performed and the overall readability/quality of the PL is acceptable. The final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline/Clavulaanzuur DSM Sinochem 875 mg/125 mg, powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 875 mg/125 mg powder for oral suspension. Augmentin 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, both under fasting and fed conditions.

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/Clavulaanzuur DSM Sinochem powder for oral suspension with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 October 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