CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amoxicilline DSM Sinochem Pharmaceuticals 250 mg and 500 mg capsules, hard
DSM Sinochem Pharmaceuticals Netherlands B.V., The Netherlands

amoxicillin trihydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1768/001-002/DC
Registration number in the Netherlands: RVG 112291 - 112292

3 October 2013

Pharmacotherapeutic group:	ß-lactam antibacterials, penicillins with broad spectrum.
ATC code:	J01CA04
Route of administration:	oral
Therapeutic indication:	treatment or prophylaxis of bacterial infections caused by amoxicillin-susceptible gram-positive and gram-negative pathogens
Prescription status:	prescription only
Date of authorisation in NL:	19 July 2013
Concerned Member States:	Decentralised procedure with IE and FR (500 mg only)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

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 Pharmaceuticals 250 mg and 500 mg capsules, hard, from DSM Sinochem Pharmaceuticals Netherlands B.V. The date of authorisation was on 19 July 2013 in the Netherlands.

The product is indicated for the oral treatment or prophylaxis of the following bacterial infections caused by amoxicillin-susceptible gram-positive and gram-negative pathogens:

Treatment
- Acute otitis media,
- Acute bacterial sinusitis (adequately diagnosed),
- Group A beta-haemolytic streptococcal tonsillitis,
- Acute exacerbation of chronic bronchitis,
- Community-acquired pneumonia,
- Cystitis,
- Early localized Lyme disease associated with erythema migrans (stage 1),
- *Helicobacter pylori* eradication: in appropriate combination with another antibacterial agent and an appropriate ulcer healing agent in adult patients with *H. pylori* associate peptic ulcers.

Prophylaxis
- Prophylaxis of endocarditis, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

A comprehensive description of the indications and posology is given in the SPC.

Amoxicillin is an aminobenzyl penicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Amoxil® 250 mg and 500 mg, capsules (NL License RVG 06497 and 06498) which has been registered in The Netherlands by GlaxoSmithKline B.V. since 1972 (original product). In addition, reference is made to Amoxil authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Amoxil® 500 mg, capsules, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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 granulated powder, which is soluble in water, very slightly soluble in alcohol, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

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 European Pharmacopoeia.

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 particle size, tapped density, microbiological quality and heavy metals. Certificates of analysis of three batches have been provided, showing compliance to the specification.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 72 months. Based on the data submitted, a retest period could be granted of six years when stored in a polyethylene bag placed in a sealed laminate bag in a carton box.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Amoxicilline DSM Sinochem Pharmaceuticals 250 mg are hard gelatin capsules with red cap and white body, cylindrical, with rounded ends, smooth, opaque and uniform surface, filled with white to off white granular powder. The capsule is 18.8 to 19.4 mm long and approximately 6.91 mm wide.
Amoxicilline DSM Sinochem Pharmaceuticals 500 mg are hard gelatin capsules with red cap and white body, cylindrical, with rounded ends, smooth, opaque and uniform surface, filled with white to off white granular powder. The capsule is 21.0 to 21.6 mm long and approximately 7.64 wide.

The capsules are packed in blister packs of transparent PVC heat sealed to aluminium foil.

The excipients are:
Capsule content: talc, magnesium stearate.

Capsule shell: gelatin, quinoline yellow (E104), allura red (E129), titanium dioxide (E171), silicon dioxide, sodium laurilsulfate, glacial acetic acid, glycerol.

The two strengths are dose proportional.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is discussed and their functions explained. During development, design of experiments was applied to achieve the final formulation, but no design space or proven acceptable ranges are claimed or granted. The pharmaceutical development of the product has been adequately performed. Comparative in-vitro dissolution data between the 500 mg test and reference product and between the 250 mg and 500 mg test product have been demonstrated. The biowaiver for the 250 mg capsule is justified on quality grounds.

Manufacturing process
The manufacturing process concerns a standard process which involves the mixing of the drug substance with talc and magnesium stearate and subsequent filling in the premade capsules and finally packaging. The manufacturing process has been adequately validated on three full scale batches 250 mg and 500 mg.

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 and are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification (by HPLC and UV), uniformity of dosage units, water content, average mass, dissolution, related substances, assay and microbiological purity. The release and end-of shelf-life specifications are identical with the exception of the limit for total impurities. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data has been presented for three full scale batches per strength, including the bio-batch, demonstrating compliance with the specification as proposed.

Stability of drug product
Stability data on the drug product has been provided on three full scaled batches per strength stored at 25°C/60% RH (18 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-Al blisters. The results of the stability studies show an increase of impurities at both storage conditions, which is more pronounced at accelerated conditions. All impurities remain well within the specified limits. Photostability studies showed that the capsules are not sensitive to light. No light protection is necessary for the drug product. Based on the stability data presented a shelf-life of 24 months can be granted. The storage condition ‘Store below 25°C’ is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is of animal origin. Certificates of suitability have been submitted for the suppliers of the gelatin. The TSE risk is considered to be covered.

II.2 Non-clinical aspects

This product is a generic formulation of Amoxil® 250 mg and 500 mg, capsules, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amoxicillin trihydrate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Amoxicillin trihydrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Amoxicilline DSM Sinochem Pharmaceuticals 500 mg capsules, hard is compared with the pharmacokinetic profile of the reference product Amoxil® 500 mg, capsules.

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

Design
A single-dose, 2-way crossover bioequivalence study was carried out under fasted conditions in 26 healthy male (13) and female (13) subjects, aged 20-35 years. Each subject received a single dose (500 mg) of one of the 2 amoxicillin trihydrate formulations. The capsule was orally administered with 200 ml water after an overnight fast. Fasting was continued for 4 h after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 and 16.0 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

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 before start of Period II. Twenty-five subjects completed the study and were included in the statistical analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	18945 ± 3897	19287 ± 3921	5826 ± 1564	1.8 ± 0.8	1.1 ± 0.1
Reference	19761 ± 4016	20080 ± 3972	6460 ± 2196	1.8 ± 0.7	1.1 ± 0.2
***Ratio (90% CI)**	0.96 (0.90 – 1.02)	-	0.92 (0.83 – 1.01)	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$	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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of amoxicillin trihydrate under fasted conditions, it can be concluded that Amoxicilline DSM Sinochem Pharmaceuticals 500 mg capsules and the Amoxil® 500 mg, capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
A biowaiver is accepted for the 250 mg strength on the following grounds:
- The capsules are manufactured by the same manufacturing process.
- The formulations are dose proportional.
- Amoxicillin show linear pharmacokinetics.
- Dissolution data of the two strengths are comparable.

Risk management plan
Amoxicillin trihydrate was first approved in 1972, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amoxicillin trihydrate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for other Amoxicillin trihydrate containing products. Further, the outcome of the article 45 Paediatric Worksharing SE/W/0009/PdWS/001 was implemented in the text.

Readability test
Readability testing was performed on the package leaflet.
The test was developed to ensure potential users of Amoxicillin could trace, comprehend and act on the information in the PIL. Fifteen questions were drafted using mostly hypothetical questions, with additional questions as “what would you do” to verify that the participant comprehended the information as to make the correct decision. Key Safety issues were properly covered in the test. Four other questions were posed to obtain feedback on good, bad points, design and level of difficulty overall.

The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. No revision was done after the pilot test. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In the first round of testing the data showed the correct section was traced to answer the question, on 100% of the time. The same result was achieved where each question

was answered correctly 100% of the time. In the second round of testing the correct answer was found and understood in 99.5% of the time. No suggestions for revision were made.
The readability test has been sufficiently performed.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amoxicilline DSM Sinochem Pharmaceuticals 250 mg and 500 mg capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Amoxil® 250 mg and 500 mg, capsules. Amoxil® 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other amoxicillin trihydrate containing products.

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 Pharmaceuticals 250 mg and 500 mg capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 July 2013. Amoxicilline DSM Sinochem Pharmaceuticals 250 mg and 500 mg capsules, hard is authorised in the Netherlands on 19 July 2013.

The date for the first renewal will be: 4 July 2018.

The following post-approval commitments have been made during the procedure:

- Amoxicillin is nominated for an article 30 referral. This implies that in due time all indications will be subject to a thorough review with regard to the benefit –risk balance considering current knowledge with regard to the benefit and risk and the antimicrobial susceptibility.
  The MAH committed to amend the product information to the outcome of that referral.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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