

Public Assessment Report

Scientific discussion

**Amoxicilline/Clavulaanzuur STADA 500/125 mg,
film-coated tablets**

(Amoxicillin trihydrate/Clavulanic acid)

NL/H/2745/001/DC

Date: 7 July 2014

This module reflects the scientific discussion for the approval of Amoxicilline/Clavulaanzuur STADA 500/125 mg, film-coated tablets. The procedure was finalised on 28 January 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amoxicilline/Clavulaanzuur STADA 500/125 mg, film-coated tablets from Stada Arzneimittel AG.

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, 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 500/125 mg film-coated tablets (NL license RVG 09840) which has been registered in the Netherlands by GlaxoSmithKline BV since 2 December 1983. In addition, reference is made to Augmentin authorisations in the individual member states (reference product).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Amoxicilline/Clavulaanzuur STADA 500/125 mg is an oblong, white to slightly yellowish film-coated tablet, embossed on one side with GG N6. Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

The tablets are packed in Al/Al blister packs.

The excipients are:

Tablet core - colloidal anhydrous silica, magnesium stearate, sodium starch glycolate (type A) and cellulose microcrystalline.

Tablet coating - triethyl citrate, hypromellose, talc, ethylcellulose, cetyl alcohol, sodium lauryl sulphate and titanium dioxide.

II.2 Drug Substances

The active substances are amoxicillin trihydrate and potassium clavulanate. Both are established active substances described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white 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 European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing processes have been included.

Quality control of drug substance

The drug substance specifications are in line with the Ph.Eur. and the CEP without any additional tests. 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 specification have been provided for three batches of each drug substance.

Stability of drug substance

Amoxicillin trihydrate

Stability data on this active substance have been provided for three full-scaled batches stored at 25°-30°C (60 months) and 40°C/75% RH (6 months), and on three full-scale batches that were only stored at 25-30°C (24-48 months). Stability data on three full-scale batches stored at 30°C/65% RH (up to 24 months) have also been provided. At both storage conditions all tested parameters remain within the specified limits. The proposed retest period of 60 months with storage condition 'Store below 30°C' is justified.

Potassium clavulanate

Stability data on the active substance have been provided for six full-scale batches that were stored at 2-8°C (24 months) and 25°C/60% RH (6 months). Stability data have also been provided for three full-scale batches in a different container that were stored at 2-8°C (36 months) and 25°C/60% RH (6 months). At both storage conditions all parameters remained within the specified limits. The proposed retest period of 24 months and storage conditions 'Store in a refrigerator (at 2-8°C)' and 'Keep container tightly closed in order to protect from light and humidity' are justified.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients are well known. The main development study performed was the comparative dissolution studies between the test and reference product used in the bioequivalence studies. Although it could not be fully demonstrated that the results of the comparative *in vitro* dissolution reflect bioequivalence as demonstrated *in vivo*, the latter prevails. The choices of the packaging and manufacturing process are justified. The test batch used in the bioequivalence studies was manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process mainly consists of preparation of granules containing amoxicillin (by wet granulation), mixing with the other components and the potassium clavulanate, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, dissolution, uniformity of dosage units, water content, related substances, microbial purity and assay. Except for the limits for related substances and assay, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three full-scale batches stored at 25°C/60% RH (24 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 Al-Al blister strips. An increase in impurities is seen at both storage conditions as well as a decrease in assay of both active substances. The storage claim that the drug product should be protected from light and moisture is justified, based on the moisture sensitivity of clavulanic acid and the statement in the BP co-amoxiclav tablets monograph that the product should be protected from light. Based on the provided data, the proposed shelf-life of 24 months and storage condition 'Store below 25°C, store in the original package in order to protect from light and moisture' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSE statements have been provided for both active substances. The starting material of amoxicillin trihydrate is 6-aminopenicillanic acid (6-APA). Lactose is used as a starting material in the fermentation of penicillin to manufacture 6-APA. The lactose suppliers confirmed that the milk is sourced from healthy animals fit for human consumption and that no other ruminant material, with the exception of calf rennet, is used in the manufacturing process. The calf rennet complies to the public statement EMA/CPMP/571/02.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amoxicilline/Clavulaanzuur STADA 500/125 mg 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/Clavulaanzuur STADA 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 Augmentin, 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 has submitted two bioequivalence studies, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Amoxicilline/Clavulaanzuur STADA 500/125 mg (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Augmentin 500/125 mg film-coated tablets (GSK, Austria), under fasting and fed conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula 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 bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I – fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions in 68 healthy male (31) and female (37) subjects, aged 23-75 years. Each subject received a single dose (500 mg amoxicillin, 125 mg clavulanic acid) of one of the 2 formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours 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, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 10.0 hours after administration of the products.

Results

All sixty-eight subjects completed the study. In accordance with the protocol, data of 68 subjects were included in the pharmacokinetic and statistical analysis for clavulanic acid and data of the first 34 subjects completing the study were included in the pharmacokinetic and statistical analysis for amoxicillin. This is acceptable.

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

Treatment N=34	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	25806 \pm 5586	26036 \pm 5699	9125 \pm 2766	1.5 (1.0 – 4.0)	1.4 \pm 0.2
Reference	25971 \pm 5429	26201 \pm 5525	9263 \pm 2752	1.5 (1.0 – 4.0)	1.4 \pm 0.2
*Ratio (90% CI)	1.00 (0.96 – 1.02)	--	0.99 (0.91 – 1.07)	--	--
CV (%)	7.7	--	19.4	--	--
AUC_{0-∞} 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					

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of clavulanic acid under fasting conditions.

Treatment N=68	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
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Test	8359 ± 3074	8503 ± 3091	3613 ± 1320	1.25 (0.75 – 2.50)	1.2 ± 0.2
Reference	8370 ± 3643	8505 ± 3666	3565 ± 1428	1.17 (0.75 – 3.0)	1.2 ± 0.2
*Ratio (90% CI)	1.04 (0.96 – 1.13)	--	1.04 (0.95 – 1.13)	--	--
CV (%)	29.9	--	31.2	--	--
AUC_{0-∞} 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					

**In-transformed values*

Conclusion on bioequivalence study II

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/Clavulaanzuur STADA 500/125 mg is considered bioequivalent with Augmentin 500/125 mg film-coated tablets under fasting conditions.

The study design was a single-dose, crossover study under fasting conditions. However, as stated in the SmPC, 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. In view of this, the member states commented that in this case a bioequivalence study should be carried out under fed conditions, as bioavailability is optimised under these conditions and can be considered more sensitive for detection of differences between two formulations. The MAH submitted the results of a second bioequivalence study, conducted under fed conditions, which are presented below.

Bioequivalence study II – under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 70 healthy male (31) and female (39) subjects, aged 19-71 years. Each subject received a single dose (500 mg amoxicillin, 125 mg clavulanic acid) of one of the 2 formulations. The tablets were administered in solid form with 240 ml water before intake of a high fat, high caloric meal. The breakfast consisted of 2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 ml of whole milk. Subjects were required to start their meal as soon as it was served and to complete it in 30 minutes or less. For each subject 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, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 10.0 hours after administration of the products.

The single-dose, crossover study under fed conditions meets the requirement of the applicable guidelines and is in accordance with the recommendation stated in the SmPC.

Results

Two subjects were withdrawn as they could not finish their meal in time and 1 subject was withdrawn because of vomiting within 3 hours after dosing. Sixty-seven subjects completed the study. In accordance with the protocol, these 67 subjects were included in the pharmacokinetic and statistical analysis for clavulanic acid, and 33 subjects for amoxicillin. This is acceptable.

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

Treatment N=33	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
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Test	21205 ± 5361	21448 ± 5456	8915 ± 2549	1.25 (0.75 – 4.0)	1.4 ± 0.3
Reference	22362 ± 5708	22615 ± 5869	8998 ± 2419	1.25 (1.0 – 2.5)	1.4 ± 0.2
*Ratio (90% CI)	0.95 (0.92 – 0.98)	--	0.99 (0.93 – 1.05)	--	--
CV (%)	7.6	--	14.8	--	--
AUC_{0-∞} 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					

**In-transformed values*

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

Treatment N=67	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	8662 ± 2425	8789 ± 2440	4030 ± 1013	1.0 (0.57 – 2.0)	1.2 ± 0.2
Reference	8475 ± 2411	8602 ± 2422	3890 ± 1044	1.25 (0.75 – 2.25)	1.2 ± 0.2
*Ratio (90% CI)	1.02 (0.98 – 1.07)	--	1.04 (0.98 – 1.09)	--	--
CV (%)	15.6	--	18.8	--	--
AUC_{0-∞} 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					

**In-transformed values*

Conclusion on bioequivalence study II

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/ Clavulaanzuur STADA 500/125 mg is considered bioequivalent with Augmentin 500/125 mg film-coated tablets under fed conditions. In addition, the results of the fasting study and the fed study were comparable, *i.e.* showing no food effect.

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 submitted a statement on the absence of a Risk Management Plan, and indicated that the application concerns a generic product, for which the active ingredient has been in use for many years, and has a well-established safety profile. The member states considered this acceptable, as submission of a Risk Minimisation Plan was not required yet when this application was made. Routine pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product is authorized.

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 a

bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product under both fasted and fed conditions. There are no product specific pharmacovigilance issues. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH submitted a bridging report making reference to the harmonized originator package leaflet (PL) for Augmentin, for which an Article 30 Referral procedure was finalised (EMEA/H/A-30/979). In addition, for the lay out/design waiver, the MAH submitted a detailed statement concerning the established house style layout. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline/Clavulaanzuur STADA 500/125 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 500/125 mg film-coated tablets. 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.

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 STADA 500/125 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 January 2014. The product was authorised in the Netherlands on 3 March 2014.

There were no post-approval commitments made during the procedure.

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