

Public Assessment Report

Scientific discussion

**Amoxicilline/Clavulaanzuur Regiomedica
250 mg/62.5 mg/5 ml and 400 mg/57 mg/5 ml
powder for oral suspension**

**(amoxicillin trihydrate and potassium
clavulanic)**

NL/H/3561/001-002/DC

Date: 10 February 2017

This module reflects the scientific discussion for the approval of Amoxicilline/Clavulaanzuur Regiomedica 250 mg/62.5 mg/5 ml and 400 mg/57 mg/5 ml powder for oral suspension. The procedure was finalised on 7 July 2016. 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/Clavulaanzuur Regiomedica 250 mg/62.5 mg/5 ml and 400 mg/57 mg/5 ml powder for oral suspension from Regiomedica GmbH.

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 products Augmentan 250 mg/62.5 mg/5 ml, powder for oral suspension and Augmentan 400 mg/57 mg/5 ml, powder for oral suspension that were authorised in Germany on 18 September 1986 and 10 May 1999 respectively. The German products are used as European Reference Product. In the Netherlands only the reference product Augmentin 100 mg/12.5 mg/ml (or 500 mg/62.5 mg/5 ml) is registered as well as several generics of the 250 mg/62.5 mg/5 ml powder for oral suspension. No 400 mg/57 mg/5 ml product strengths are available on the Dutch market.

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

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 a white to creamy white powder for oral suspension presented in two strengths (250 mg/62.5 mg/5 ml and 400 mg/57 mg/5 ml).

The powder for oral suspension is packed in an amber coloured glass bottle of 125 ml or 200 ml closed with a child-resistant, tamper evident polypropylene screw cap with aluminium foil liner.

After reconstitution with water the medicinal product is a white to creamy white suspension. 5 ml of suspension contains amoxicillin trihydrate equivalent to 250 mg or 400 mg amoxicillin and potassium clavulanate equivalent to 62.5 mg or 57 mg of clavulanic acid.

The excipients are silicon dioxide, microcrystalline cellulose, carmellose sodium, sucralose, sodium citrate anhydrous, citric acid anhydrous, silica colloidal anhydrous, mannitol, xanthan gum, vanilla flavour (maize maltodextrin, triacetin E1518, modified corn starch E1450, vanillin, myrrh absolute (commiphora molmol), isopentanol) and tutti frutti flavour (maize maltodextrin, polylyene glycol E1520, benzyl alcohol, orange oil (citrus sinensis), vanillin and ethyl butyrate).

II.2 Drug Substances

The active substances are amoxicillin trihydrate and potassium clavulanate, which are established active substances described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is white or almost white crystalline powder, which is slightly soluble in water. Potassium clavulanate is a white or almost white hygroscopic powder, which is freely soluble in water, slightly soluble in ethanol and very soluble in acetone. 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 have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances

The active substance specification for amoxicillin trihydrate is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for related substances, particle size and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

The active substance specification for potassium clavulanate is in line with the Ph.Eur. monograph on diluted potassium clavulanate, with additional tests for any unspecified impurity and residual solvents according to the requirements stated on the CEP as well as a test for microbial quality. The specification is acceptable. Batch analysis data on two batches of potassium clavulanate diluted have been provided, demonstrating compliance with the drug substance specification.

Stability of drug substances

Amoxicillin trihydrate is stable for 6 years and diluted potassium clavulanate is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEPs 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 justified and their functions explained. The main development studies performed were the characterisation of the EU reference products, optimisation of the product composition to match the pH, viscosity and dissolution profiles of the reference products, investigation of the impact of particle size on the drug product release, studies to confirm the instructions for reconstitution and studies to evaluate the particle size distribution, sedimentation and resuspendability of the suspension. A stability overage for potassium clavulanate is applied in the drug product. The pharmaceutical development of the product has been adequately performed.

A bioequivalence study has been performed for both product strengths versus the corresponding reference product strengths. Confirmatory *in vitro* dissolution studies showed similar dissolution for both active substances between the bioequivalence study test and reference batches at different pH levels within the physiological range. The drug product batches used in the bioequivalence studies were manufactured according to the finalised composition and manufacturing process.

Manufacturing process

The main steps of the manufacturing process are the mixing of the components and filling into bottles. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled bulk batches for both product strengths in accordance with the relevant European guidelines. The product is

manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.)

Control of excipients

The excipients comply with Ph.Eur., United States Pharmacopoeia National Formulary (USP-NF) or in-house specifications. 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 description (before and after reconstitution), viscosity, water content (before reconstitution), fill weight (before reconstitution), pH, identity, dissolution, assay, deliverable volume, uniformity of mass of delivered doses, related substances, clavulanate polymer and other fluorescent products, and microbial quality. Except for water content, viscosity, and clavulanic acid assay the release and shelf-life requirements are identical. For clavulanate polymer and other fluorescent products a separate in-use shelf life limit for the reconstituted solution was set. The analytical methods have been adequately described and validated. 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 packed batches of each fill volume for both strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three pilot scale batches of bulk product for both strengths that were filled in each of the intended bottle volumes and quantities. The batches were stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in upright as well as inverted position. An acceptable bracketing design was applied for the stability studies. Results of a photostability study performed on the drug product in its primary packaging after reconstitution showed that the primary packaging sufficiently protects the product from light. Based on the study results the claimed shelf-life of 24 months with storage conditions "Store in the original package in order to protect from light and moisture" and "This medicinal product does not require any special temperature storage conditions" are justified.

Stability data has been provided demonstrating that the product remains stable for 7 days following reconstitution, when stored in a refrigerator (2-8°C). The study was repeated on batches that had first been stored for different periods at long-term, intermediate or accelerated storage conditions. The study results on batches after storage were comparable. The claimed in-use period of 7 days for the product when stored in a refrigerator (2-8°C) is justified.

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amoxicilline/Clavulaanzuur Regiomedica 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 powder for oral solution 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 are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Amoxicilline/Clavulaanzuur Regiomedica powder for oral suspension (Regiomedica GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Augmentin powder for oral suspension (GlaxoSmithKline):

- Study I - A bioequivalence study under fed conditions with the 250 mg/62.5 mg/5 ml strength
- Study II - A bioequivalence study under fed conditions with the 400 mg/57 mg/5 ml strength

The choice of the UK (250 mg/62.5 mg/5 ml strength) and Austrian (400 mg/57 mg/5 ml) reference products in the bioequivalence studies has been justified. 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 this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I - Amoxicillin/Clavulaanzuur Regiomedica 250 mg/62.5 mg/5 ml vs Augmentin under fed conditions

Design

A single-dose, two-way, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 22-44 years. Each subject received a single dose (250 mg amoxicillin and 62.5 mg clavulanic acid) of both the test and the reference amoxicillin/clavulanic acid formulations. The powder was suspended in 5 ml water before intake. The suspension was orally administered with

240 ml water 30 minutes after serving of a standardised high-calorie and high-fat breakfast. There were 2 dosing periods, separated by a washout period of 10 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, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. It is in line with the SmPC of Augmentin, stating that the dose should be administered at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid. Although the formulation was administered within 30 min after start of intake of the breakfast, this can be considered at start of the meal.

Results

Four subjects were withdrawn due to protocol violation. Therefore 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of 250 mg amoxicillin under fed conditions.

Treatment N=36	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	15.78 ± 2.60	15.94 ± 2.58	4.79 ± 1.20	1.5 (1.0 – 2.75)	1.3 ± 0.1
Reference	15.49 ± 2.19	15.63 ± 2.19	4.82 ± 1.14	1.38 (0.75 – 2.5)	1.3 ± 0.1
*Ratio (90% CI)	1.02 (0.99 – 1.04)	--	0.99 (0.95 – 1.03)	--	--
CV (%)	6.2	--	10.3	--	--
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 CV coefficient of variation					

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of 62.5 mg clavulanic acid under fed conditions.

Treatment N=36	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	2.45 ± 0.79	2.48 ± 0.79	1.08 ± 0.37	1.25 (0.75 – 2.25)	1.1 ± 0.1
Reference	2.28 ± 0.65	2.30 ± 0.65	0.98 ± 0.33	1.25 (1.0 – 2.0)	1.0 ± 0.1
*Ratio (90% CI)	1.05 (0.96 – 1.15)	--	1.08 (0.99 – 1.18)	--	--
CV (%)	22.9	--	22.5	--	--
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 CV coefficient of variation					

**In-transformed values*

Bioequivalence study II- Amoxicillin/Clavulaanzuur Regiomedica 400 mg/57 mg/5 ml vs Augmentin under fed conditions

Design

A single-dose, two-way, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 18-41 years. Each subject received a single dose (400 mg amoxicillin and 57 mg clavulanic acid) of both the test and the reference amoxicillin/clavulanic acid formulations. The powder was suspended in 5 ml water before intake. The suspension was orally administered with 240 ml water 30 minutes after serving of a standardised high-calorie and high-fat breakfast. 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, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. It is in line with the SmPC of Augmentin, stating that the dose should be administered at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid. Although the formulation was administered within 30 min after start of intake of the breakfast, this can be considered at start of the meal.

Results

One subject was discontinued post-dose period I on medical ground, as he had an adverse event (vomiting). Four subjects were standby, not dosed and checked out from the facility. Therefore 35 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 400 mg amoxicillin under fed conditions.

Treatment N=35	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	23.86 ± 5.06	24.07 ± 5.17	7.18 ± 1.55	1.5 (1.0 – 3.0)	1.4 ± 0.2
Reference	23.69 ± 5.37	23.90 ± 5.49	7.63 ± 1.63	1.25 (1.0 – 4.0)	1.5 ± 0.3
*Ratio (90% CI)	1.01 (0.99 – 1.02)	--	0.94 (0.91 – 0.97)	--	--
CV (%)	4.2	--	8.1	--	--
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 CV coefficient of variation					

**In-transformed values*

Table 4 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 57 mg clavulanic acid under fed conditions.

Treatment N=35	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	2.58 ± 0.80	2.61 ± 0.80	1.07 ± 0.32	1.25 (0.75 – 2.25)	1.1 ± 0.2
Reference	2.62 ± 0.84	2.65 ± 0.84	1.10 ± 0.34	1.25 (0.75 – 3.5)	1.1 ± 0.2
*Ratio (90% CI)	0.99 (0.94 – 1.04)	--	0.98 (0.91 – 1.05)	--	--
CV (%)	12.8	--	17.4	--	--

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
CV	coefficient of variation

**In-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 Amoxicilline/Clavulaanzuur Regiomedica powder for oral suspension is considered bioequivalent with Augmentin powder for oral suspension.

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/Clavulaanzuur Regiomedica powder for oral suspension.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> • Hypersensitivity • Hepatic impairment
Important potential risks	<ul style="list-style-type: none"> • Acute generalised exanthematous pustulosis (AGEP) • Antibiotic-associated colitis • Increased risk of neonatal necrotising 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	<ul style="list-style-type: none"> • Exposure during pregnancy • Exposure through human milk • Exposure in children under 2 month of age

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 powder for oral suspension. 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 3 participants, followed by two rounds with 10 participants each. A total number of 19 questions were asked. 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/Clavulaanzuur Regiomedica powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 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.

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 Regiomedica 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 July 2016.

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