COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg film-coated tablets

(amoxicillin trihydrate and potassium clavulanate)

NL/H/4272/001-002/DC

Date: 1 August 2019

This module reflects the scientific discussion for the approval of Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg film-coated tablets. The procedure was finalised at 6 March 2019. 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 Polpharma 500 mg/125 mg and 875 mg/125 mg film-coated tablets from Pharmaceutical Works Polpharma S.A.

The product is indicated for the treatment of the following infections in adults and children (see SmPC sections 4.2, 4.4 and 5.1):

- 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 500 mg/125 mg (UK/H/4738/001) and 875 mg/125 mg film-coated tablets (DE/H/2868/002) authorised in The Netherlands on 2 December 1983 and 22 August 1996 respectively, by GlaxoSmithKline B.V. It is noted that the marketing authorisation of Augmentin 875 mg/125 mg film-coated tablets in The Netherlands was withdrawn in December 2013.

The concerned member states (CMS) involved in this procedure were Lithuania, Latvia and Poland.

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 off white oblong film-coated tablet with score line that is available in two strengths.

The product contains as active substance 500 mg or 875 mg of amoxicillin, as 573.95 mg or 1004.40 mg of amoxicillin trihydrate. Both strengths also contain as active substance 125 mg clavulanic acid, as 297.81 mg potassium clavulanate diluted with microcrystalline cellulose (1:1).

The film-coated tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are:
Tablet core - microcrystalline cellulose (E460), crospovidone Type A (E1202), croscarmellose sodium (E468), colloidal anhydrous silica (E551), and magnesium stearate (E470b).
Film-coating - titanium dioxide (E171), talc (E553b), macrogol 6000 (E1521), and basic butylated methacrylate copolymer.

II.2 Drug Substances

Amoxicillin trihydrate
The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white crystalline powder. The active substance is slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in fatty oils. It dissolves in diluted acids and diluted 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets

the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for six years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Potassium clavulanate
The active substance is potassium clavulanate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. Potassium clavulanate is freely soluble in water, slightly soluble in ethanol (96%), very slightly soluble in acetone. For potassium clavulanate the CEP procedure is used. The copies of three CEP's have been provided.

Manufacturing process
CEP's have 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. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches of each manufacturer.

Stability of drug substance
Stability data on the active substance from manufacturer-I have been provided for three full scaled batches stored at 5°C (48 months) and 25°C/60% RH (6 months). No significant changes occurred. The proposed retest period of 48 months and storage condition '2-8°C under nitrogen, in the original package' are justified.

The active substance from manufacturer-II is stable for 48 months when stored in triple polyethylene bags (under nitrogen atmosphere, with silica gel bags in between) in a cellopolial thermos-sealed bag placed in a polyethylene drum. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

Stability data on the active substance from manufacturer-III have been provided for three full scaled batches stored at 5°C (24 months) and 25°C/60% RH (6 months). No significant changes occurred. The proposed retest period of 24 months and storage condition '2-8°C under nitrogen, in the original package' are justified.

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 development focused mainly on obtaining optimal disintegrant concentration. The choices of the packaging and manufacturing process are sufficiently justified. The tablets contain a score line only to facilitate breaking for ease of swallowing and not to divide into equal doses. Pharmaceutical development of the product has been adequately performed.

Four bioequivalence studies have been performed to demonstrate bioequivalence between Amoxicilline/Clavulaanzuur Polpharma and Augmentin, two studies per strength. The two reference biobatches are considered acceptable. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Considering that both active substances, amoxicillin (class I) and clavulanic acid (class III) have a fast or very fast dissolution in the different media, the discriminatory power of the dissolution method did not need to be demonstrated.

Manufacturing process

The manufacturing process consists of three separate roller compaction steps. Amoxicillin is processed with part of the excipients in one step, clavulanic acid (mixture with microcrystalline cellulose) is processed with part of the excipients in another step, and both active pharmaceutical ingredients are combined with remaining excipients in a third step. The manufacturing processes are slightly different for the two strengths, due to the amount of amoxicillin trihydrate contained in the different strengths.
The products are manufactured using conventional manufacturing techniques. The manufacturing processes have been adequately validated according to relevant European guidelines, and process validation data on the products have been presented for three full scaled batches, per strength.

Control of excipients

The excipients comply with the Ph.Eur. requirements. 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, identity, average mass, assay of amoxicillin, assay of potassium clavulanate, uniformity of dosage units, dissolution test, water content, degradation products, residual solvents, clavulanic acid polymeric impurities and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The tightened dissolution limit for amoxicillin is acceptable.

The analytical methods have been adequately described; it has been shown that the method for related substances is stability indicating. The possible presence of elemental impurities was evaluated in accordance with ICH Q3D. Batch analytical data have been provided on seven full scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for seven full scaled batches per strength, stored at 25°C/60% RH (either 36 months or 18 months), 30°C/65% RH (12 months) and 40°C/75% RH (either three months or six months). The conditions used in the stability studies are according to the ICH stability guideline. Some batches went out of specification for the clavulanic acid assay either during long-term, intermediate or accelerated conditions. On the basis of statistical analysis, a tighter release assay limit is found appropriate to guarantee that the content of clavulanic acid in the drug product will remain stable within a shelf-life limit of 24 months if batch release takes place at the lower release limit (i.e. that not more than 7 % degradation will take place during the shelf-life). Therefore, the new limit is acceptable. Also it is concluded that the tighter limit proposed for the assay of clavulanic acid is sufficient to guarantee that the dissolution limit of clavulanic acid of NLT 85 % is met at 24 months. This is also supported by the available stability data. This is considered sufficient to guarantee that the dissolution limit of the drug product at the end of shelf life is met. The dissolution limit for amoxicillin was revised to NLT 85% (Q) in 20 minutes. Compliance at the end of the proposed shelf life (24 months) under long term storage for two batches per strength was demonstrated. Given the absence of photostability study, the storage claim should include 'protect from light'.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition is "Do not store above 25°C. Store in the original Al-Al-blister in order to protect from light and moisture."

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amoxicilline/Clavulaanzuur Polpharma 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 Polpharma 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 four bioequivalence studies, which are discussed below. Hence for each strength a bioequivalence study under fasting and fed condition is submitted.

IV.2 Pharmacokinetics

The MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test product Amoxicilline/Clavulaanzuur Polpharma (Pharmaceutical Works Polpharma S.A., Poland) is compared with the pharmacokinetic profile of the reference product Augmentin film-coated tablets (GSK, Belgium):

- Study I - A bioequivalence study under fasting conditions with the 500 mg/125 mg strength

- Study II - A bioequivalence study under fasting conditions with the 875 mg/125 mg strength
- Study III - A bioequivalence study under fed conditions with the 500 mg/125 mg strength
- Study IV - A bioequivalence study under fed conditions with the 875 mg/125 mg strength

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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 studies

Bioequivalence study I – Amoxicillin/Clavulaanzuur Polpharma 500 mg/125 mg vs Augmentin under fasting conditions (C13172)
Design
A single-dose, randomized, balanced, open-label, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-42 years. Each subject received a single dose (500 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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, 6.5, 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. A single dose, crossover study under fasting conditions was carried out. However 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. As such, the 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. As a result, the MAH carried out also a study under fed conditions (study C14292).

Results
Four subjects did not report to the facility for Period II check in. Therefore, 36 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=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	30307 ± 7285	30599 ± 7307	9026 ± 2530	1.83 (0.83 - 4.0)	1.6 ± 0.3
Reference	30923 ± 5864	31267 ± 5858	9049 ± 2449	1.92 (1.0 - 5.0)	1.8 ± 0.4
***Ratio (90% CI)**	0.97 (0.92 - 1.02)	--	0.99 (0.93 - 1.06)	--	--
CV (%)	13.9	--	16.6	--	--

$AUC_{0-\infty}$ 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 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fasted 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	7886 ± 2627	8210 ± 2297	3136 ± 1221	1.5 (0.83 - 3.0)	1.1 ± 0.7
Reference	8310 ± 2979	8399 ± 2987	3382 ± 1451	1.42 (0.5 - 4.0)	1.2 ± 0.2
***Ratio (90% CI)**	0.98 (0.88 - 1.08)	--	0.96 (0.85 - 1.09)	--	--
CV (%)	25.8	--	32.2	--	--

$AUC_{0-\infty}$ 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*

For amoxicillin and clavulanic acid, four samples were reanalysed for aberrant value. The original values were replaced by the repeated obtained values. As reanalysis for pharmacokinetic reasons may bias the study outcome, the MAH should have used the original values and recalculate the pharmacokinetics and the statistics. On request additional

reanalysis data have been submitted, and by using the original values, bioequivalence under fasting conditions could still be proven (see Table 3 and Table 4 below).

Table 3.

For Amoxicillin acid:

Parameters (Units)	Ratio of Geometric Least Squares Means			Intra Subject CV %	90% Confidence Limits (%)	Power %
	Test product (A)	Reference product (B)	(A / B) %		(A vs. B)	
C_{max} (ng/mL)	8797.992	8686.955	101.3	16.7	94.81-108.19	100.0
AUC_{0-t} (ng. hr/mL)	29396.412	30257.331	97.2	13.9	91.92-102.68	100.0
AUC_{0-inf} (ng. hr/mL)	29694.815	30610.652	97.0	13.9	91.81-102.51	100.0

Table 4.

For Clavulanic acid:

Parameters (Units)	Ratio of Geometric Least Squares Means			Intra Subject CV %	90% Confidence Limits (%)	Power %
	Test product (A)	Reference product (B)	(A / B) %		(A vs. B)	
C_{max} (ng/mL)	3026.782	3076.453	98.4	35.6	85.60-113.08	84.3
AUC_{0-t} (ng. hr/mL)	7634.925	7783.229	98.1	26.0	88.49-108.74	97.2
AUC_{0-inf} (ng. hr/mL)	7732.698	7876.561	98.2	25.8	88.63-108.74	97.3

Bioequivalence study II – Amoxicillin/Clavulaanzuur Polpharma 500 mg/125 mg vs Augmentin under fed conditions (C14294)

Design

A single-dose, randomized, 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 20-44 years. Each subject received a single dose (500 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The tablet was orally administered with 240 ml water. The tablets were administered 30 minutes after the start of intake of a high fat, high calorie, non-vegetarian breakfast (911 kcal). There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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, 6.5, 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. A single dose, crossover study under fed conditions was carried out, in accordance with the SmPC of Augmentin at time the studies were carried

out, 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.

Results

Two subjects did not report to facility for Period II check in. One subject withdrew from the study prior to period II. Therefore, 37 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin under fed conditions.

Treatment N=37	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	28570 ± 5675	29008 ± 5843	9167 ± 2523	2.0 (1.33 - 5.5)	1.6 ± 0.4
Reference	28777 ± 5268	29097 ± 5328	9399 ± 2832	2.0 (1.33 - 4.0)	1.7 ± 0.4
***Ratio (90% CI)**	0.99 (0.96 - 1.02)	--	0.99 (0.91 - 1.07)	--	--
CV (%)	7.5	--	20.6	--	--

$AUC_{0-\infty}$ 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 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fed conditions.

Treatment N=37	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5450 ± 2332	5528 ± 2335	2318 ± 1082	1.83 (1.33 - 4.0)	1.1 ± 0.2
Reference	5613 ± 2177	5695 ± 2184	2301 ± 1076	1.83 (1.0 - 4.0)	1.1 ± 0.2
***Ratio (90% CI)**	0.94 (0.81 - 1.09)	--	0.98 (0.82 - 1.18)	--	--
CV (%)	38.5	--	47.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Based on the submitted bioequivalence study C14294 with the 500 mg/125 mg tablet, the Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg tablet is considered bioequivalent with the Augmentin 500 mg/125 mg tablet under fed conditions.

Bioequivalence study III – Amoxicillin/Clavulaanzuur Polpharma 875 mg/125 mg vs Augmentin under fasting conditions (C13148)

Design

A single-dose, randomized, 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 19-43 years. Each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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. A single dose, crossover study under fasting conditions was carried out. However 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. As such, the 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. As a result, the MAH carried out also a study under fed conditions (study C14293).

Results

One subject did not report to facility for Period II check in. Therefore, 39 subjects were eligible for pharmacokinetic analysis.

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 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	40827 ± 9795	41259 ± 9893	11802 ± 2820	2.0 (1.0 - 4.5)	1.6 ± 0.3
Reference	42337 ± 10522	42696 ± 10612	11833 ± 3425	2.5 (1.0 - 4.55)	1.6 ± 0.2
***Ratio (90% CI)**	1.05 (0.84 - 1.32)	--	1.08 (0.89 - 1.31)	--	--

CV (%)	63.8	--	55.0	--	--

$AUC_{0-\infty}$ 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 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	8880 ± 3931	8967 ± 3938	3577 ± 1783	1.5 (0.83 - 4.0)	1.2 ± 0.2
Reference	7985 ± 3613	8073 ± 3613	3342 ± 1664	1.5 (0.67 - 3.0)	1.2 ± 0.2
***Ratio (90% CI)**	1.22 (0.91 - 1.63)	--	1.11 (0.86 - 1.42)	--	--
CV (%)	89.5	--	71.8	--	--

$AUC_{0-\infty}$ 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*

Based on the pharmacokinetic parameters of amoxicillin and clavulanic acid, the reference and test are considered not bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and C_{max} were not inside the normal range of acceptability (0.80 – 1.25). However, it appeared that one subject had very low plasma concentrations for amoxicillin as well as for clavulanic acid, indicating that the tablet was not swallowed by the subject. As the AUC_t value of this subject is below 5% of the geometric mean of the total population without this subject, it is acceptable to exclude the data of this subject from pharmacokinetic and statistical analysis.

The results for amoxicillin and clavulanic acid without the results of this outlier are shown in Table 9 and Table 10.

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin under fasted conditions, excluding one outlier.

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	40883 ± 9920	41319 ± 10019	11723 ± 2813	2.0 (1.0 - 4.5)	1.6 ± 0.3
Reference	43442 ± 8049	43808 ± 8136	12138 ± 2882	2.5 (1.0 - 4.55)	1.6 ± 0.2
***Ratio (90% CI)**	0.93 (0.86 - 1.00)	--	0.96 (0.89 - 1.03)	--	--
CV (%)	20.3	--	18.5	--	--

$AUC_{0-\infty}$ 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 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fasted conditions, excluding one outlier.

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	8812 ± 3961	8898 ± 3967	3520 ± 1772	1.6 (0.83 - 1.6)	1.2 ± 0.8
Reference	8195 ± 3413	8283 ± 3412	3428 ± 1596	1.5 (0.67 - 3.0)	1.2 ± 0.2
***Ratio (90% CI)**	1.05 (0.89 - 1.22)	--	0.99 (0.84 - 1.15)	--	--
CV (%)	41.8	--	42.1	--	--

$AUC_{0-\infty}$ 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*

Based on the pharmacokinetic parameters of amoxicillin and clavulanic acid, excluding the outlier, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Bioequivalence study IV – Amoxicillin/Clavulaanzuur Polpharma 875 mg/125 mg vs Augmentin under fed conditions (C14293)

Design

A single-dose, randomized, 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 20-42 years. Each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The tablet was orally administered with 240 ml water. The tablets were administered 30 minutes after the start of intake of a high fat, high calorie, non-vegetarian breakfast (911 kcal). There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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, 6.5, 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. A single dose, crossover study under fed conditions was carried out, in accordance with the SmPC of Augmentin at time the studies were carried out, 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.

Results

38 subjects were eligible for pharmacokinetic analysis.

Table 11. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin under fed conditions.

Treatment N=38	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	44339 ± 8276	45063 ± 8148	12772 ± 4138	2.25 (1.5 - 6.0)	1.6 ± 0.3
Reference	45599 ± 8032	46193 ± 8287	13068 ± 2935	2.5 (1.33 - 5.5)	1.6 ± 0.3
***Ratio (90% CI)**	0.97 (0.92 - 1.01)	--	0.94 (0.86 - 1.03)	--	--
CV (%)	12.1	--	24.8	--	--

$AUC_{0-\infty}$ 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 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fed conditions.

Treatment N=38	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5333 ± 2467	5436 ± 2473	2160 ± 1168	2.0 (1.33 - 5.0)	1.2 ± 0.3
Reference	5351 ± 2716	5433 ± 2713	2131 ± 1234	2.0 (1.33 - 4.5)	1.1 ± 0.2
***Ratio (90% CI)**	1.01 (0.87 - 1.18)	--	1.02 (0.85 - 1.22)	--	--
CV (%)	41.6	--	49.1	--	--

$AUC_{0-\infty}$ 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*

Based on the pharmacokinetic parameters of amoxicillin and clavulanic acid, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Pre-dose samples should not contain the active substances. However two pre-dose samples taken in Period I were found to contain amoxicillin. The levels were below 5% of C_{max}. No clear explanation could be given. The MAH submitted on request new calculations, excluding these two subjects. Bioequivalence could still be proven (see Table 13 and Table 14 below).

Table 13.

For amoxicillin:

Parameters (Units)	Ratio of Geometric Least Squares Means			Intra Subject CV %	90% Confidence Limits (%)	Power (%)
	Test Product (A)	Reference Product (B)	(A/B) %		(A vs. B)	
C_{max} (ng/ml)	12069.235	12747.939	94.7	25.4	85.69-104.60	97.8
AUC_{0-t} (ng.hr/ml)	43599.288	44647.842	97.7	12.2	93.04-102.49	100.0
AUC_{0-inf} (ng.hr/ml)	44417.782	45194.865	98.3	11.0	94.06-102.69	100.0

Table 14.

For clavulanic acid:

Parameters (Units)	Ratio of Geometric Least Squares Means			Intra Subject CV %	90% Confidence Limits (%)	Power (%)
	Test Product (A)	Reference Product (B)	(A/B) %		(A vs. B)	
C_{max} (ng/ml)	1788.967	1741.372	102.7	50.4	84.97-124.22	61.6
AUC_{0-t} (ng.hr/ml)	4667.453	4560.943	102.3	42.7	86.90-120.51	72.9
AUC_{0-inf} (ng.hr/ml)	4782.673	4659.877	102.6	41.3	87.59-120.26	75.2

Based on the submitted bioequivalence study C14293 with the 875 mg/125 mg tablet, the Amoxicilline/Clavulaanzuur Polpharma 875 mg/125 mg tablet is considered bioequivalent with the Augmentin 875 mg/125 mg tablet under fed conditions.

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 Polpharma is considered bioequivalent with Augmentin.

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 Polpharma.

Table 15. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity (anapyslaxis and Severe cutaneous adverse reactions) • Pseudomembranous colitis, and overgrowth of non-susceptible organisms • Hepatobiliary disorders • Renal and urinary disorders • Blood and lymphatic disorders • Convulsions resulting from increased systemic exposure
Important potential risks	• Necrotizing enterocolitis in neonates, from prophylactic treatment of bacterial spread to the

	amniotic fluid, in pre-term premature rupture of the foetal membrane (pPROM)
Missing information	--

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference for the content to Augmentin (UK/H/4738/001) and for the lay-out to Ramipril/Amlodipine 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg capsules, hard (approved through a national marketing authorisation procedure in Poland). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 500 mg/125 mg and 875 mg/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

Polpharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 March 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse