COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg powder for oral suspension in sachet

(amoxicillin trihydrate and potassium clavulanate)

NL/H/4271/001-002/DC

Date: 12 September 2019

This module reflects the scientific discussion for the approval of Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg powder for oral suspension in sachet. The procedure was finalised at 3 April 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
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amoxicilline/Clavulaanzuur Polpharma 500 mg/125 mg and 875 mg/125 mg powder for oral suspension in sachet 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 products Augmentin 500 mg/125 mg powder for oral suspension and Augmentin 875 mg/125 mg powder for oral suspension that were authorised in Spain by GlaxoSmithKline S.A. on 1 January 1986 and 3 February 1993 respectively. The Spanish products are used as European Reference Product.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Amoxicilline/Clavulaanzuur Polpharma is an off white to yellowish powder. The powder is packed in polyethylene terephthalate/aluminium/polyethylene sachets.

Each sachet contains amoxicillin trihydrate equivalent to 500 mg or 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid. The contents of the single-dose sachet are to be dispersed in half a glass of water and stirred well. The appearance of the suspension after preparation is an off-white to cream coloured suspension with strawberry flavour.

The excipients are:
- Crospovidone type A
- Silica, colloidal anhydrous
- Aspartame (E951)
- Magnesium stearate
- Strawberry flavour (maltodextrin, triethyl citrate (E1505), flavouring components, propylene glycol (E1520))

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

Amoxicillin trihydrate 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 main focus during the development was on the flow characteristics of the powder mass. The choices of the packaging and manufacturing process are sufficiently justified. 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.

Manufacturing process

The manufacturing process selected consists mixing the two active substances with the excipients, in two steps, and filling the powder into sachets. The products are manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

With the exception of the strawberry flavour the excipients comply with the Ph.Eur. requirements. For the strawberry flavour an acceptable in-house specification has been provided. 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, uniformity of filling mass, assay of amoxicillin, assay of potassium clavulanate, uniformity of dosage units, water content, degradation products, 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.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches per strength, stored at 25°C/60% RH (36 months), 30°/65% RH (12 months) and 40°C/75% RH (6 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 and amoxicillin assay during the storage under accelerated conditions. Given the known sensitivity to moisture, the product should be stored in the original package. The polyethylene terephthalate/aluminium/polyethylene sachet will protect the drug product from light.
On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “Do not store above 25°C. Store in the original package in order to protect from moisture.”

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

Oleic acid of animal origin has been used in the manufacturing process of potassium clavulanate. TSE statements have been provided. No other 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 for 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 for 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. 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 powder for oral suspension (GSK, Spain):

- 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

Study C13303: single dose fasting; 500 mg/125 mg powder for oral suspension
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 21-39 years. Each subject received a single dose (500 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The powder was suspended in water before intake after an overnight fast. The content of the sachet was poured into a container with approximately 20 ml of water and stirred until the formation of suspension. Subjects were instructed to drink the whole suspension, and the container was rinsed for three times with the remaining water 220 ml (240 – 20 = 220 ml). There were two dosing periods, separated by a washout period of nine 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 after administration of the products.

The design of the study is acceptable. However, as stated in the SmPC of Augmentin at time of carrying out the study, 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 C15114).

Results

Two subjects did not report to facility for Period II check in. Therefore 38 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=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	28868 ± 6455	29165 ± 6542	9081 ± 2024	1.5 (0.83 – 3.5)	1.7 ± 0.4
Reference	30360 ± 4912	30626 ± 4956	9804 ± 2433	1.5 (0.67 – 3.0)	1.7 ± 0.5
***Ratio (90% CI)**	0.94 (0.90 – 0.99)	--	0.93 (0.87 – 1.01)	--	--
CV (%)	12.6	--	19.9	--	--

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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fasted 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	8461 ± 2642	8557 ± 2648	3540 ± 1210	1.0 (0.67 – 4.5)	1.2 ± 0.2
Reference	8758 ± 2740	8847 ± 2740	3614 ± 1229	1.0 (0.50 – 3.5)	1.2 ± 0.3
***Ratio (90% CI)**	0.99 (0.91 – 1.07)	--	0.99 (0.91 – 1.09)	--	--

CV (%)	20.5	--	23.8	--	--

$AUC_{0-\infty}$ 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*

Study C15114: single dose fed; 500 mg/125 mg powder for oral suspension

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, 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 powder was suspended in water before intake. The content of the sachet was poured into a container with approximately 20 ml of water and stirred until the formation of suspension. Subjects were instructed to drink the whole suspension, and the container was rinsed for three times with the remaining water 220 ml (240 – 20 = 220 ml). The suspensions were administered were administered 30 minutes after the start of intake of a high fat, high calorie, non-vegetarian breakfast. There were two dosing periods, separated by a washout period of nine 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 after administration of the products.

The 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 were withdrawn in Period I due to adverse events. Three subjects did not report to the clinical site for Period II. Therefore, 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	28297 ± 4442	29793 ± 8370	7201 ± 1620	2.0 (1.33 – 6.0)	2.0 ± 2.1
Reference	28532 ± 4857	28966 ± 5066	7362 ± 1684	1.83 (1.0 – 4.5)	1.6 ± 0.3

***Ratio (90% CI)**	0.99 (0.96 – 1.03)	--	0.98 (0.92 – 1.05)	--	--
CV (%)	9.1	--	16.2	--	--

$AUC_{0-\infty}$ 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*

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

Treatment N=35	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	4539 ± 1560	4630 ± 1577	1680 ± 582	1.83 (0.83 – 2.5)	1.2 ± 0.3
Reference	4574 ± 1665	4673 ± 1693	1725 ± 596	1.67 (1.0 – 3.0)	1.2 ± 0.3
***Ratio (90% CI)**	1.00 (0.94 – 1.07)	--	0.98 (0.90 – 1.05)	--	--
CV (%)	16.0	--	20.0	--	--

$AUC_{0-\infty}$ 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*

Study C13302: single dose fasting; 875 mg/125 mg powder for oral suspension

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-39 years. Each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The powder was suspended in water before intake after an overnight fast. The content of the sachet was poured into a container with approximately 20 ml of water and stirred until the formation of suspension. Subjects were instructed to drink the whole suspension, and the container was rinsed for three times with the remaining water 220 ml (240 – 20 = 220 ml). There were two dosing periods, separated by a washout period of nine 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 after administration of the products.

The design of the study is acceptable. However, as stated in the SmPC of Augmentin at time of carrying out the study, 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 C15113).

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

Table 5. 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	47485 ± 9773	47946 ± 9932	13165 ± 3305	2.0 (0.83 – 3.5)	1.7 ± 0.3
Reference	47055 ± 11501	47452 ± 11607	13861 ± 4201	1.67 (1.0 – 4.5)	1.7 ± 0.4
***Ratio (90% CI)**	1.02 (0.96 – 1.08)	--	0.97 (0.90 – 1.03)	--	--
CV (%)	15.0	--	16.8	--	--

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

**ln-transformed values*

Table 6. 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	8130 ± 2435	8218 ± 2446	3620 ± 1261	1.0 (0.67 – 3.0)	1.2 ± 0.3
Reference	8434 ± 2539	8521 ± 2545	3668 ± 1262	1.0 (0.67 – 2.0)	1.2 ± 0.3
***Ratio (90% CI)**	0.97 (0.90 – 1.04)	--	0.98 (0.90 – 1.07)	--	--
CV (%)	18.9	--	22.9	--	--

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

**ln-transformed values*

Study C15113: single dose fed; 875 mg/125 mg powder for oral suspension

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-39 years. Each subject received a single dose (875 mg amoxicillin and 125 mg clavulanic acid) of one of the two formulations. The powder was suspended in water before intake. The content of the sachet was poured into a container with approximately 20 ml of water and stirred until the formation of suspension. Subjects were instructed to drink the whole suspension, and the container was rinsed for three times with the remaining water 220 ml (i.e. 240 – 20 = 220 ml). The suspensions were administered were administered 30 minutes after the start of intake of a high fat, high calorie, non-vegetarian breakfast. There were two dosing periods, separated by a washout period of nine 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 after administration of the products.

The 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

Three subjects were withdrawn in Period I due to adverse events. One subject did not report to the clinical site for Period II. Therefore, 36 subjects were eligible for pharmacokinetic analysis.

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

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

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

**ln-transformed values*

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

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

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

**ln-transformed values*

<u>Conclusion on bioequivalence studies</u>

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 studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Amoxicilline/Clavulaanzuur Polpharma.

Table 9. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity (anaphylaxis 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	• None

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 and for the lay-out to Aston PPH 5 mg/20 mg, 5 mg/10 mg, 10 mg/20 mg, 10 mg/10 mg

capsules, hard (PL/H/0399/001-004/DC). 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 powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 500 mg/125 mg and 875 mg/125 mg powder for oral suspension. Augmentin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 3 April 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