Public Assessment Report

Decentralised Procedure

Co-amoxiclav 250 mg/125 mg Film-coated Tablets
Co-amoxiclav 500 mg/125 mg Film-coated Tablets

(Clavulanic acid and amoxicillin)

Procedure No: UK/H/6278/001-2/DC

UK Licence Number: PL 20117/0280-1

Morningside Healthcare Ltd.
LAY SUMMARY

Co-amoxiclav 250 mg/125 mg Film-coated Tablets
Co-amoxiclav 500 mg/125 mg Film-coated Tablets
(amoxicillin 250 mg or 500 mg, clavulanic acid 125 mg, film-coated tablet)

This is a summary of the Public Assessment Report (PAR) for Co-amoxiclav 250 mg/125 mg Film-coated Tablets (PL 20117/0280; UK/H/6278/001/DC) and Co-amoxiclav 500 mg/125 mg Film-coated Tablets (PL 20117/0281; UK/H/6278/002/DC). It explains how Co-amoxiclav 250 mg/125 mg and 500 mg/125 mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Co-amoxiclav 250 mg/125 mg and 500 mg/125 mg Film-coated Tablets.

The products will be collectively referred to as Co-amoxiclav throughout the remainder of this public assessment report (PAR).

For practical information about using Co-amoxiclav, patients should read the package leaflet or contact their doctor or pharmacist.

What is Co-amoxiclav and what is it used for?
Co-amoxiclav is a ‘generic medicine’. This means that Co-amoxiclav is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK).

Co-amoxiclav 250 mg/125 mg Film-coated Tablets are used in adults and children to treat the following infections:
- Sinus infections
- Urinary tract infections
- Skin infections
- Dental infections.

Co-amoxiclav 500 mg/125 mg Film-coated Tablets are used in adults and children to treat the following infections:
- Middle ear and sinus infections
- Respiratory tract infections
- Urinary tract infections
- Skin and soft tissue infections including dental infections
- Bone and joint infections.

How does Co-amoxiclav work?
Co-amoxiclav is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called amoxicillin and clavulanic acid. Amoxicillin belongs to a group of medicines called ‘penicillins’ that can sometimes be stopped from working (made inactive). The other active component (clavulanic acid) stops this from happening.

How is Co-amoxiclav used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth).

The patient must always take this medicine exactly as their doctor has told them. The patient should
check with their doctor or pharmacist if they are not sure.

The usual dose of this medicine is:

**Adults and children weighing 40 kg and over**
- The usual dose is 1 tablet three times a day.

**Children weighing less than 40 kg**
*Co-amoxiclav 250 mg/125 mg Film-coated Tablets:*
Co-amoxiclav 250 mg/125 mg Film-coated Tablets are not recommended for use in children weighing less than 40 kg.
Children aged 6 years or less should preferably be treated with amoxicillin/clavulanic acid oral suspension or sachets.

*Co-amoxiclav 500 mg/125 mg Film-coated Tablets:*
Children aged 6 years or less should preferably be treated with amoxicillin/clavulanic acid oral suspension or sachets.

The patient’s carer should ask the patient’s doctor or pharmacist for advice when giving Co-amoxiclav 500 mg/125 mg Film-coated Tablets to children weighing less than 40 kg. Co-amoxiclav 500 mg/125 mg Film-coated Tablets are not suitable for children weighing less than 25 kg.

**Patients with kidney and liver problems**
- If the patient has kidney problems the dose might be changed. A different strength or a different medicine may be chosen by their doctor.
- If the patient has liver problems they may have more frequent blood tests to check how their liver is working.

**How to take Co-amoxiclav**
- Swallow the tablets whole with a glass of water at the start of a meal or slightly before. The higher strength tablet (Co-amoxiclav 500 mg/125 mg Film-coated Tablet) can be broken along the score line to make it easier to swallow. The patient must take both pieces of the tablet at the same time.
- Space the doses evenly during the day, at least 4 hours apart. Do not take 2 doses in 1 hour.
- Do not take Co-amoxiclav for more than two weeks. If the patient still feels unwell they should go back to see the doctor.

**If the patient stops taking Co-amoxiclav**
The patient should keep taking Co-amoxiclav until the treatment is finished, even if they feel better. The patient needs every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Co-amoxiclav is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.
What benefits of Co-amoxiclav have been shown in studies?
Because Co-amoxiclav is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Co-amoxiclav?
Because Co-amoxiclav is a generic medicine and is bioequivalent to the reference medicine Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Co-amoxiclav, see section 4 of the package leaflet available on the MHRA website.

Why was Co-amoxiclav approved?
It was concluded that, in accordance with EU requirements, Co-amoxiclav has been shown to have comparable quality and to be bioequivalent to Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK). Therefore, the MHRA decided that, as for Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK); the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Co-amoxiclav?
A risk management plan (RMP) has been developed to ensure that Co-amoxiclav is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Co-amoxiclav including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Co-amoxiclav
Malta and the UK agreed to grant Marketing Authorisations for Co-amoxiclav on 28 June 2016. Marketing Authorisations were granted in the UK on 26 July 2016.

The full PAR for Co-amoxiclav follows this summary.

For more information about treatment with Co-amoxiclav, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Ltd, marketing authorisations for the medicinal product Co-amoxiclav (PL 20117/0280-1; UK/H/6278/001-2/DC) The product is a prescription-only medicine (POM) indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1 of the SmPC):

Co-amoxiclav 250 mg/125 mg Film-coated Tablets:
- Acute bacterial sinusitis (adequately diagnosed)
- Cystitis
- Pyelonephritis
- Cellulitis
- Animal bites
- Severe dental abscess with spreading cellulitis.

Co-amoxiclav 500 mg/125 mg Film-coated Tablets:
- 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.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Augmentin 375 mg Tablets (PL 00038/0270) which was first authorised in the UK to Beecham Group plc (trading as GlaxoSmithKline UK or Beecham Research) on 03 April 1981 and Augmentin 500 mg/125 mg film-coated tablets which was first authorised in the Netherlands to GlaxoSmithKline BV on 02 December 1993. The equivalent UK reference product for the 500 mg/125 mg strength is Augmentin 625 mg Tablets (PL 00038/0362; Beecham Group plc)

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBP) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.
Two bioequivalence studies (conducted under fasting conditions) were submitted to support these applications. The applicant has stated that the bioequivalence studies were conducted in accordance with the IEC approved protocol, protocol amendments, relevant SOPs, ICH ‘Guidance on Good Clinical Practice’ E6[R 1](1996), Principles of Good Laboratory Practice, Declaration of Helsinki (Brazil, October-2013), Schedule Y (amended version 2013) of The Drugs and Cosmetics Act, CDSCO guidelines (Guideline for Bioavailability and Bioequivalence studies), ICMR guidelines for biomedical research on human participants(2006), EMA guidelines (Guideline on the investigation of bioequivalence, 20 Jan 2010), all other applicable regulatory agencies & relevant SOPs required for the conduct of the studies and to meet the ethical requirements of Directive 2001/20/EC.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 28 June 2016. After a subsequent national phase, a licence was granted in the UK on 26 July 2016.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains amoxicillin trihydrate equivalent to 250 mg or 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid as the active ingredients. Other ingredients consist of the pharmaceutical excipients:

**Tablet core:**
Microcrystalline cellulose (E460) [250 mg/125 mg strength only], crospovidone Type A (E1202), croscarmellose sodium (E468), colloidal anhydrous silica (E551) and magnesium stearate (E470b).

**Film-coating:**
Basic butylated methacrylate copolymer, titanium dioxide (E171), talc (E553b) and macrogol 6000.

The finished product is packaged in OPA/Al/PVC-Al blister packs and is available in pack sizes of 4, 5, 6, 10, 12, 14, 16, 18, 20, 21, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 100 and 500 film-coated tablets. The 500 mg/125 mg tablet strength is also available in a pack size of 15 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances

1. **Amoxicillin trihydrate**
   INN: Amoxicillin trihydrate
   Chemical name: \((2S,5R,6R)-6-[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

   Structure:
   ![Structure of Amoxicillin Trihydrate](image)

   Molecular formula: \(C_{16}H_{19}N_{3}O_{5}S_3\cdot3H_2O\)
   Molecular weight: 419.4 g/mol
   Description: White or almost white crystalline powder.
   Solubility: Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

   Amoxicillin trihydrate is the subject of a European Pharmacopoeia monograph.

   All aspects of the manufacture and control of the active substance, amoxicillin trihydrate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

2. **Potassium clavulanate**
   INN: Potassium clavulanate
   Chemical name: Potassium \((2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate\).
Structural formula:

\[ \text{Molecular formula: } C_8H_8KNO_5 \]
\[ \text{Molecular mass: } 237.3 \text{ g/mol} \]
\[ \text{Appearance: } \text{A white or almost white crystalline powder.} \]
\[ \text{Solubility: } \text{Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone.} \]

Potassium clavulanate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, potassium clavulanate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing amoxicillin trihydrate equivalent to 250 mg or 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid per tablet, that are generic versions of the reference product Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The applicant has committed to perform process validation on three consecutive batches of the product for commercial batch size and a satisfactory process validation scheme has been submitted.
Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25°C. Store in the original package in order to protect from moisture.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III  NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of clavulanic acid and amoxicillin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Co-amoxiclav 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.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of clavulanic acid and amoxicillin is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of clavulanic acid and amoxicillin.

Based on the data provided, Co-amoxiclav can be considered bioequivalent Augmentin 375 mg and 625 mg Tablets (Beecham Group plc, UK).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1
An open label, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant’s test product Co-amoxiclav 250 mg/125 mg Film-coated Tablets (Morningside Healthcare Ltd) versus the reference product Augmentin 375 mg Tablets (Beecham Group plc, UK) in healthy, adult, subjects under fasting conditions.

The design of the study and the population chosen were acceptable. There has been a debate at European level whether bioequivalence studies for amoxicillin/ clavulanic acid should be conducted in the fed or fasting state. After review of the available data, the Pharmacokinetics Working Party (PKWP) decided in quarter 4 of 2015 that fed studies are required in principle; however studies in the fasted state may be
accepted. The RMS agrees to accepting the fasted study here as literature data, albeit not unequivocally, suggest no relevant food effect, and fasted studies have been accepted repeatedly in the past. Inclusion and exclusion criteria were presented and acceptable. The randomisation scheme was provided.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 250/125mg tablet) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

**Table: Summary of Pharmacokinetic data for amoxicillin:**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Ratio of Geometric Least Squares Means</th>
<th>Intra Subject CV %</th>
<th>90% Confidence Limits (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test product (A)</td>
<td>Reference product (B)</td>
<td>(A / B) %</td>
<td>(A vs. B)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>4657.001</td>
<td>4620.454</td>
<td>100.8</td>
<td>24.0</td>
</tr>
<tr>
<td>AUC_{0-t} (ng. hr/mL)</td>
<td>14490.190</td>
<td>13964.537</td>
<td>103.8</td>
<td>11.2</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng. hr/mL)</td>
<td>14664.637</td>
<td>14158.935</td>
<td>103.6</td>
<td>11.2</td>
</tr>
</tbody>
</table>

**Table: Summary of Pharmacokinetic data for clavulanic acid:**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Ratio of Geometric Least Squares Means</th>
<th>Intra Subject CV %</th>
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<td>Reference product (B)</td>
<td>(A / B) %</td>
<td>(A vs. B)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>2655.688</td>
<td>2499.376</td>
<td>106.3</td>
<td>39.5</td>
</tr>
<tr>
<td>AUC_{0-t} (ng. hr/mL)</td>
<td>6566.290</td>
<td>6087.753</td>
<td>107.9</td>
<td>33.3</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng. hr/mL)</td>
<td>6651.499</td>
<td>6174.733</td>
<td>107.7</td>
<td>32.7</td>
</tr>
</tbody>
</table>

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for amoxicillin and clavulanic acid lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Co-amoxiclav 250 mg/125 mg Film-coated Tablets (Morningside Healthcare Ltd) is bioequivalent to the reference product Augmentin 375 mg Tablets (Beecham Group plc, UK).

**STUDY 2**

An open label, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant’s test product Co-amoxiclav 500 mg/125 mg Film-coated Tablets (Morningside Healthcare Ltd) versus the reference product Augmentin 625 mg Tablets (Beecham Group plc, UK) in healthy, adult, subjects under fasting conditions.
The design of the study and the population chosen were acceptable. There has been a debate at European level whether bioequivalence studies for amoxicillin/ clavulanic acid should be conducted in the fed or fasting state. After review of the available data, the Pharmacokinetics Working Party (PKWP) decided in quarter 4 of 2015 that fed studies are required in principle, however studies in the fasted state may be accepted. The RMS agrees to accepting the fasted study here as literature data, albeit not unequivocally, suggest no relevant food effect, and fasted studies have been accepted repeatedly in the past. Inclusion and exclusion criteria were presented and acceptable. The randomisation scheme was provided.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 500/125mg tablet) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

**Table: Summary of Pharmacokinetic data for amoxicillin:**

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<td></td>
<td>Test product (A)</td>
<td>Reference product (B)</td>
<td>(A / B) %</td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>8643.039</td>
<td>8703.574</td>
<td>99.3</td>
<td>16.6</td>
</tr>
<tr>
<td>AUC_{0-4} (ng hr/mL)</td>
<td>29364.469</td>
<td>30292.397</td>
<td>96.9</td>
<td>13.9</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng hr/mL)</td>
<td>29662.952</td>
<td>30645.528</td>
<td>96.8</td>
<td>13.9</td>
</tr>
</tbody>
</table>

AUC_{0-4} area under the plasma concentration-time curve from zero to t hours  
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity  
C_{max} maximum plasma concentration

**Table: Summary of Pharmacokinetic data for clavulanic acid:**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
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<td>Test product (A)</td>
<td>Reference product (B)</td>
<td>(A / B) %</td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>2959.204</td>
<td>3076.453</td>
<td>96.2</td>
<td>32.2</td>
</tr>
<tr>
<td>AUC_{0-4} (ng hr/mL)</td>
<td>7623.691</td>
<td>7791.433</td>
<td>97.8</td>
<td>25.8</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng hr/mL)</td>
<td>7721.549</td>
<td>7884.823</td>
<td>97.9</td>
<td>25.6</td>
</tr>
</tbody>
</table>

AUC_{0-4} area under the plasma concentration-time curve from zero to t hours  
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity  
C_{max} maximum plasma concentration

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for amoxicillin and clavulanic acid lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Co-amoxiclav 500 mg/125 mg Film-coated Tablets (Morningside Healthcare Ltd) is bioequivalent to the reference product Augmentin 625 mg Tablets (Beecham Group plc, UK).
IV.3 **Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 **Clinical efficacy**
No new efficacy data were submitted and none were required for applications of this type.

IV.5 **Clinical safety**
No new safety data were submitted and none are required.

IV.6 **Risk Management Plan (RMP) and Pharmacovigilance System**
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Co-amoxiclav.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

**Summary table of safety concerns:**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>• Hypersensitivity &amp; anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>• Severe haematological reactions (neutropenia, thrombocytopenia, agranulocytosis)</td>
</tr>
<tr>
<td></td>
<td>• Interaction with oral anticoagulants &amp; prolongation of prothrombin time</td>
</tr>
<tr>
<td></td>
<td>• Antibiotic-associated diarrhoea (including pseudomembranous and haemorrhagic colitis)</td>
</tr>
<tr>
<td></td>
<td>• Interaction with methotrexate &amp; methotrexate toxicity</td>
</tr>
<tr>
<td></td>
<td>• Allergic skin reactions with concomitant allopurinol</td>
</tr>
<tr>
<td></td>
<td>• Severe skin reactions (EM, SJS, TEN &amp; AGEP)</td>
</tr>
<tr>
<td></td>
<td>• Convolusions in impaired renal function or with high dosages</td>
</tr>
<tr>
<td></td>
<td>• Crystalluria</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of neonatal necrotising enterocolitis (when amoxicillin/clavulanic acid is used prophylactically in women with preterm, premature rupture of the foetal membrane)</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>• None</td>
</tr>
<tr>
<td>Important missing information</td>
<td>• Exposure during pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Exposure through human milk</td>
</tr>
<tr>
<td></td>
<td>• Exposure in children with a body weight of less than 40 kg</td>
</tr>
</tbody>
</table>
Summary of planned risk minimisation activities:

<table>
<thead>
<tr>
<th>Safety concerns</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimisation activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity &amp; anaphylaxis</td>
<td>Routine pharmacovigilance activities are considered sufficient and no further actions are required.</td>
<td>Risks are adequately described in the product information. No further risk management activities are proposed.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe haematological reactions (neutropenia, thrombocytopenia, agranulocytosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with oral anticoagulants &amp; prolongation of prothrombin time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic associated diarrhoea (including pseudomembranous and haemorrhagic colitis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with methotrexate &amp; methotrexate toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic skin reactions with concomitant allopurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe skin reactions (EM, SJS, TEN &amp; AGEP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions in impaired renal function or with high dosages</td>
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<td></td>
</tr>
</tbody>
</table>

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Amoxicillin/clavulanic acid DSM Sinochem 500 mg/125mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amoxicillin and clavulanic acid is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is as follows:
Co-amoxiclav
500mg/125mg Film-coated Tablets
Amoxicillin
Clavulanic acid

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500mg/125mg Film-coated Tablets
Amoxicillin
Clavulanic acid

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Morningside Healthcare Ltd.
MC599HMA/2015/001