Public Assessment Report

Decentralised Procedure

CO-AMOXICLAV 250MG/125MG FILM-COATED TABLETS
CO-AMOXICLAV 500MG/125MG FILM-COATED TABLETS

Procedure No: UK/H/3244/001-2/DC

UK Licence No: PL 25298/0007-8

BROWN AND BURK UK LIMITED
LAY SUMMARY

On 23 December 2011, the MHRA granted Brown and Burk UK Limited Marketing Authorisations (licences) for the medicinal products Co-amoxiclav 250mg/125mg and 500mg/125mg Film-coated Tablets (PL 25298/0007-8). These are prescription-only medicines, containing two different medicines called amoxicillin and clavulanic acid, and are used to treat the following infections in adults and children:

250mg/125mg film-coated tablets:
- Sinus infections
- Urinary tract infections
- Skin infections
- Dental infections

500mg/125mg film-coated tablets:
- Middle ear and sinus infections
- Respiratory tract infections
- Urinary tract infections
- Skin and soft tissue infections, including dental infections
- Bone and joint infections

Amoxicillin belongs to a group of medicines called “penicillins” that sometimes can be stopped from working (made inactive). The other active component, clavulanic acid, stops this from happening.

No new or unexpected safety concerns have arisen from these applications and it was, therefore, concluded that the benefits of taking Co-amoxiclav 250mg/125mg and 500mg/125mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6 Steps taken after initial procedure
## Module 1

| **Product Name** | Co-Amoxiclav 250mg/125mg Film-Coated Tablets  
Co-Amoxiclav 500mg/125mg Film-Coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Amoxicillin trihydrate and potassium clavulanate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>250mg or 500mg amoxicillin (as amoxicillin trihydrate) and 125mg clavulanic acid (as potassium clavulanate)</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Brown &amp; Burk UK Ltd, 5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ, United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Ireland, Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3244/001-2/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 1 December 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav 250mg/125mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 250mg amoxicillin as amoxicillin trihydrate and 125mg of clavulanic acid as potassium clavulanate diluted

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White colored capsule shaped film coated tablet debossed with ‘I 05’ on one side and plain on other side. Tablet length = 16.70 ± 0.10mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Co-amoxiclav is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1).
• Acute bacterial sinusitis (adequately diagnosed)
• Cystitis
• Pyelonephritis
• Cellulitis
• Animal bites
• Severe dental abscess with spreading cellulitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Co-amoxiclav that is selected to treat an individual infection should take into account:
• The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
• The severity and the site of the infection
• The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Co-amoxiclav (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Co-amoxiclav provides a total daily dose of 750 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Co-amoxiclav is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

Treatment should not be extended beyond 14 days without review.

Adults and children ≥ 40 kg
One 250 mg/125 mg tablet taken three times a day.

Children < 40 kg
Co-amoxiclav 250 mg/125 mg film-coated tablets are not recommended in children < 40 kg.

Elderly
No dose adjustment is considered necessary.
Renal impairment
Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

<table>
<thead>
<tr>
<th>CrCl: 10-30 ml/min</th>
<th>250 mg/125 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt; 10 ml /min</td>
<td>250 mg/125 mg once daily</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Two doses of 250 mg/125 mg every 24 hours, plus two doses of 250 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)</td>
</tr>
</tbody>
</table>

Children < 40 kg
In children < 40 kg with creatinine clearance less than 30 ml/min, the use of Co-amoxiclav presentations with an amoxicillin to clavulanic acid ratio of 2:1 is not recommended, as no dose adjustments are available. In such patients, Co-amoxiclav formulations with an amoxicillin to clavulanic acid ratio of 4:1 are recommended.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Co-amoxiclav is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

4.3 Contraindications
Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use
Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Co-amoxiclav is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid (e.g. penicillin-insusceptible S. pneumoniae).

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a febrile generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see Section 4.8). This reaction requires Co-amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored and appropriate adjustment made if necessary.
monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

**Methotrexate**
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

**Probenecid**
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

### 4.6 Fertility, Pregnancy and lactation

**Fertility:**
Amoxicillin/clavulanate potassium at oral doses of up to 1,200mg/kg/day was found to have no effect on fertility in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

**Pregnancy**
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the fetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

**Lactation**
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

### 4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

**Very common** ($\geq 1/10$)
**Common** ($\geq 1/100$ to $<1/10$)
**Uncommon** ($\geq 1/1,000$ to $<1/100$)
**Rare** ($\geq 1/10,000$ to $<1/1,000$)
**Very rare** ($<1/10,000$)
**Not known** (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous candidosis</td>
<td></td>
</tr>
<tr>
<td>Overgrowth of non-susceptible organisms</td>
<td>Not known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible leucopenia (including neutropenia)</td>
<td>Rare</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
</tr>
<tr>
<td>Reversible agranulocytosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Not known</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Prolongation of bleeding time and prothrombin time①</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Immune system disorders⑩</strong></td>
<td></td>
</tr>
<tr>
<td>Angioneurotic oedema</td>
<td>Not known</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Not known</td>
</tr>
<tr>
<td>Serum sickness-like syndrome</td>
<td>Not known</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reversible hyperactivity</td>
<td>Not known</td>
</tr>
<tr>
<td>Convulsions②</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Very common</td>
</tr>
<tr>
<td>Nausea①</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Antibiotic-associated colitis④</td>
<td>Not known</td>
</tr>
<tr>
<td>Black hairy tongue</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rises in AST and/or ALT⑤</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatitis⑥</td>
<td>Not known</td>
</tr>
<tr>
<td>Cholestatic jaundice⑥</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders⑦</strong></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Rare</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Not known</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>Not known</td>
</tr>
<tr>
<td>Bullous exfoliative-dermatitis</td>
<td>Not known</td>
</tr>
<tr>
<td>Acute generalised exanthemous pustulosis (AGEP)⑨</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Not known</td>
</tr>
<tr>
<td>Crystalluria⑧</td>
<td>Not known</td>
</tr>
</tbody>
</table>

① See section 4.4
② See section 4.4.
③ Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking Co-amoxiclav at the start of a meal.
④ Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
⑤ A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
⑥ These events have been noted with other penicillins and cephalosporins (see section 4.4).
⑦ If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
⑧ See section 4.9
⑨ See section 4.4
⑩ See sections 4.3 and 4.4
4.9 Overdose
Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactam inhibitors; ATC code: J01CR02.

Mode of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) 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.

PK/PD relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
• Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptibility Breakpoints (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>≤ 1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>≤ 2</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>Organism</td>
<td>Minimal</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>≤ 4</td>
</tr>
<tr>
<td><em>Streptococcus</em> A, B, C, G²</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>³</td>
<td>≤ 0.5</td>
</tr>
<tr>
<td>Enterobacteriaceae¹⁴</td>
<td>-</td>
</tr>
<tr>
<td>Gram-negative Anaerobes¹</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Gram-positive Anaerobes¹</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Non-species related breakpoints¹</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

¹ The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.
² The reported values are Oxacillin concentrations.
³ Breakpoint values in the table are based on Ampicillin breakpoints.
⁴ The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
⁵ Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

### Commonly susceptible species

**Aerobic Gram-positive micro-organisms**
- *Enterococcus faecalis*
- *Staphylococcus aureus* (methicillin-susceptible)³
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*³
- *Streptococcus pyogenes* and other beta-hemolytic streptococci
- *Streptococcus viridans* group

**Aerobic Gram-negative micro-organisms**
- *Capnocytophaga* spp.
- *Eikenella* corrodens
- *Haemophilus influenzae*²
- *Moraxella catarrhalis*
- *Pasteurella multocida*

**Anaerobic micro-organisms**
- *Bacteroides fragilis*
- *Fusobacterium nucleatum*
- *Prevotella* spp.

**Species for which acquired resistance may be a problem**

**Aerobic Gram-positive micro-organisms**
- *Enterococcus faecium* $\$

**Aerobic Gram-negative micro-organisms**
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Proteus vulgaris*

### Inherently resistant organisms
5.2 Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (250 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

<table>
<thead>
<tr>
<th>Active substance(s) administered</th>
<th>Dose (mg)</th>
<th>Cmax (µg/ml)</th>
<th>Tmax * (h)</th>
<th>AUC (0-24h) ((µg.h/ml))</th>
<th>T 1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin AMX/CA 250 mg/125 mg</td>
<td>250</td>
<td>3.3 ± 1.12</td>
<td>1.5 (1.0-2.0)</td>
<td>26.7±4.56</td>
<td>1.36 ± 0.56</td>
</tr>
<tr>
<td>Clavulanic acid AMX/CA 250 mg/125 mg</td>
<td>125</td>
<td>1.5 ± 0.70</td>
<td>1.2 (1.0-2.0)</td>
<td>12.6 ± 3.25</td>
<td>1.01 ± 0.11</td>
</tr>
</tbody>
</table>

* Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).
Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

**Biotransformation**
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

**Elimination**
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Co-amoxiclav 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

**Age**
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

**Gender**
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

**Renal impairment**
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

**Hepatic impairment**
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 **Preclinical safety data**
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Cellulose, microcrystalline (E460)
Sodium starch glycolate, Type A
Silica, colloidal anhydrous (E551)
Magnesium Stearate (E572)

**Film coat**
Titanium dioxide (E171)
Hypermellose (E464)
Polyethylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Aluminium/aluminium strips with 4/5/6/7/8/10/12/14/15/16/20/21/25/30/35/40/50/100/500 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 25298/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/12/2011

10 DATE OF REVISION OF THE TEXT
23/12/2011
1 NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav 500mg/125mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 500mg amoxicillin as amoxicillin trihydrate and 125mg of clavulanic acid as potassium clavulanate diluted

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White colored capsule shaped film coated tablet debossed with ‘1 06’ on one side and plain on other side. Tablet length = 19.40 ± 0.10mm

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Co-amoxiclav is indicated for the treatment of the following infections in adults and children (see 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
- Bone and joint infections, in particular osteomyelitis

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Co-amoxiclav that is selected to treat an individual infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of amoxicillin/clavulanic acid (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Co-amoxiclav provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of amoxicillin/clavulanic acid is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
One 500 mg/125 mg tablet taken three times a day.

Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with amoxicillin/clavulanic acid tablets, suspensions or paediatric sachets. Children aged 6 years and below should preferably be treated with amoxicillin/clavulanic acid suspension or paediatric sachets.
No clinical data are available on doses of amoxicillin/clavulanic acid 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

**Elderly**
No dose adjustment is considered necessary.

**Renal impairment**
Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

**Adults and children ≥ 40 kg**

<table>
<thead>
<tr>
<th>CrCl: 10-30 ml/min</th>
<th>500 mg/125 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt; 10 ml/min</td>
<td>500 mg/125 mg once daily</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)</td>
</tr>
</tbody>
</table>

**Children < 40 kg**

<table>
<thead>
<tr>
<th>CrCl: 10-30 ml/min</th>
<th>15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt; 10 ml/min</td>
<td>15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.</td>
</tr>
</tbody>
</table>

**Hepatic impairment**
Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

**Method of administration**
Co-amoxiclav is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally and continued with an oral preparation.

### 4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

### 4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Co-amoxiclav is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-
lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires Co-amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see section 4.2).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of
Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

4.6 Fertility, Pregnancy and lactation

Fertility:
Amoxicillin/clavulanate potassium at oral doses of up to 1,200mg/kg/day was found to have no effect on fertility in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the fetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactation
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
### PAR Co-Amoxiclav 250mg/125 and 500mg/125mg Film-Coated Tablets

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous candidosis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Overgrowth of non-susceptible organisms</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversible leucopenia (including neutropenia)</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Reversible agranulocytosis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Prolongation of bleeding time and prothrombin time¹</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioneurotic oedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Serum sickness-like syndrome</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Reversible hyperactivity</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Convulsions²</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Nausea¹</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Antibiotic-associated colitis⁴</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Black hairy tongue</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rises in AST and/or ALT³</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Hepatitis⁶</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Cholestatic jaundice⁶</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Bullous exfoliative-dermatitis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Acute generalised exanthemous pustulosis (AGEP)⁵</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Crystalluria⁸</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

¹ Prolongation of bleeding time and prothrombin time
² Convulsions
³ Rises in AST and/or ALT
⁴ Antibiotic-associated colitis
⁵ Black hairy tongue
⁶ Hepatitis
⁷ Cholestatic jaundice
⁸ Acute generalised exanthemous pustulosis (AGEP)
4.9 Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mode of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) 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.

PK/PD relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.
Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

**Breakpoints**
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenza</em>³</td>
<td>≤ 1</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em>³</td>
<td>≤ 1</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>²</td>
<td>≤ 2</td>
<td>-</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci²</td>
<td>≤ 0.25</td>
<td>-</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td><em>Enterococcus</em>³</td>
<td>≤ 4</td>
<td>8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><em>Streptococcus A, B, C, G</em>³</td>
<td>≤ 0.25</td>
<td>-</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>³</td>
<td>≤ 0.5</td>
<td>1-2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Enterobacteriaceae¹,⁴</td>
<td>-</td>
<td>-</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Gram-negative Anaerobes¹</td>
<td>≤ 4</td>
<td>8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Gram-positive Anaerobes¹</td>
<td>≤ 4</td>
<td>8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Non-species related breakpoints¹</td>
<td>≤ 2</td>
<td>4-8</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

¹ The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.
² The reported values are Oxacillin concentrations.
³ Breakpoint values in the table are based on Amoxicillin breakpoints.
⁴ The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
⁵ Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

**Commonly susceptible species**

**Aerobic Gram-positive micro-organisms**
- *Enterococcus faecalis*
- *Gardnerella vaginalis*
- *Staphylococcus aureus* (methicillin-susceptible)£
- Coagulase-negative staphylococci (methicillin-susceptible)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*³
- *Streptococcus pyogenes* and other beta-hemolytic streptococci
- *Streptococcus viridans* group

**Aerobic Gram-negative micro-organisms**
- *Capnocytophaga* spp.
- *Eikenella corrodens*
- *Haemophilus influenzae*²
- *Moraxella catarrhalis*
- *Pasteurella multocida*

**Anaerobic micro-organisms**
- *Bacteroides fragilis*
Fusobacterium nucleatum
Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms
Enterococcus faecium $^1$

Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris

Inherently resistant organisms

Aerobic Gram-negative micro-organisms
Acinetobacter sp.
Citrobacter freundii
Enterobacter sp.
Legionella pneumophila
Morganella morganii
Providencia sp.
Pseudomonas sp.
Serratia sp.
Stenotrophomonas maltophilia

Other micro-organisms
Chlamydophila pneumoniae
Chlamydophila psittaci
Coxiella burnetti
Mycoplasma pneumoniae

$^1$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
$^2$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid.
$^3$ Streptococcus pneumoniae that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4).
$^4$ Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (250 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

<table>
<thead>
<tr>
<th>Active substance(s) administered</th>
<th>Dose</th>
<th>Cmax</th>
<th>Tmax *</th>
<th>AUC (0-24h)</th>
<th>T 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>500 mg/125 mg</td>
<td>7.19 ± 2.26</td>
<td>1.5 (1.0-2.5)</td>
<td>53.5 ± 8.87</td>
<td>500</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>125 mg/125 mg</td>
<td>2.40 ± 0.83</td>
<td>1.5 (1.0-2.0)</td>
<td>15.72 ± 3.86</td>
<td>2.40 ± 0.83</td>
</tr>
</tbody>
</table>
Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

**Distribution**
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

**Biotransformation**
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

**Elimination**
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Co-amoxiclav 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

**Age**
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

**Gender**
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

**Renal impairment**
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

**Hepatic impairment**
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with Co-amoxiclav or its components.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Cellulose, microcrystalline (E460)
Sodium starch glycolate, Type A
Silica, colloidal anhydrous (E551)
Magnesium Stearate (E572)

Film coat
Titanium dioxide (E171)
Hypermellose (E464)
Polyethylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Aluminium/aluminium strips with 4/5/6/7/8/10/12/14/15/16/20/21/25/30/35/40/50/100/500 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 25298/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/12/2011

10 DATE OF REVISION OF THE TEXT
23/12/2011
Module 3

Co-amoxiclav 250mg/125mg Film-coated Tablets
Co-amoxiclav 500mg/125mg Film-coated Tablets
Amoxicillin/clavulanic acid

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Co-amoxiclav Tablets are and what they are used for
2. Before you take Co-amoxiclav Tablets
3. How to take Co-amoxiclav Tablets
4. Possible side effects
5. How to store Co-amoxiclav Tablets
6. Further information

1. WHAT CO-AMOXICLAV TABLETS ARE AND WHAT THEY ARE USED FOR

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.

Co-amoxiclav is used in adults and children to treat the following infections:

250 mg/125 mg film-coated tablets:
- sinus infections
- urinary tract infections
- skin infections
- dental infections.

500 mg/125 mg film-coated tablets:
- middle ear and sinus infections
- respiratory tract infections
- urinary tract infections

- skin and soft tissue infections including dental infections
- bone and joint infections.

2. BEFORE YOU TAKE CO-AMOXICLAV TABLETS

Do not take Co-amoxiclav:
- if you are allergic (hypersensitive) to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of Co-amoxiclav (listed in section 6)
- if you have ever had a severe allergic (hypersensitive) reaction to any other antibiotic. This can include a skin rash or swelling of the face or neck
- if you have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic.

Do not take Co-amoxiclav if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Co-amoxiclav Tablets.

Take special care with Co-amoxiclav Tablets
Talk to your doctor or pharmacist before taking this medicine if you:
- have glandular fever
- are being treated for liver or kidney problems
- are not passing water regularly.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking these tablets.

In some cases, your doctor may investigate the type of bacteria that is causing your infection. Depending on the results, you may be given a different strength of Co-amoxiclav or a different medicine.

Conditions you need to look out for:
Co-amoxiclav can make some existing conditions worse, or cause serious side effects. These include allergic reactions, convulsions (fits) and inflammation of the large intestine. You must look out for certain symptoms while you are taking Co-
amoxiclav, to reduce the risk of any problems. See 'Conditions you need to look for' in Section 4.

**Blood and urine tests:**
If you are having blood tests (such as red blood cell status tests or liver function tests) or urine tests (for glucose), let the doctor or nurse know that you are taking Co-amoxiclav. This is because Co-amoxiclav can affect the results of these types of tests.

**Using other medicines**
Please tell your doctor or pharmacist if you are using or have recently used any other medicines. This includes medicines that can be bought without a prescription and herbal medicines.

If you are taking allopurinol (used for gout) with Co-amoxiclav, it may be more likely that you'll have an allergic skin reaction.

If you are taking probenecid (used for gout), your doctor may decide to adjust your dose of Co-amoxiclav.

If medicines to help stop blood clots (such as warfarin) are taken with Co-amoxiclav Tablets then extra blood tests may be needed.

Co-amoxiclav can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works.

Antibiotics, such as Co-amoxiclav, may affect how oestrogen (the active ingredient in the contraceptive pill) is absorbed into your body. This could make the contraceptive pill less effective. As a precaution, it is advisable to use an additional form of contraception, such as a condom. You should use the additional contraceptive whilst you are taking Co-amoxiclav tablets, and for one week after you stop.

This medicine contains 0.63 mmol (or 24.632 mg) potassium per tablet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

**Pregnancy and breast-feeding**
If you are pregnant, you think you might be pregnant or if you are breast-feeding, please tell your doctor or pharmacist.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Co-amoxiclav can have side effects and the symptoms may make you unfit to drive. Don't drive or operate machinery unless you are feeling well.

### 3. HOW TO TAKE CO-AMOXICLAV TABLETS

Always take Co-amoxiclav Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Adults and children weighing 40 kg and over**

**250 mg/125 mg film-coated tablets:**
The usual dose is 1 tablet three times a day

**500 mg/125 mg film-coated tablets:**
The usual dose is 1 tablet three times a day

**Children weighing less than 40 kg**

**250 mg/125 mg film-coated tablets:**
Co-amoxiclav tablets are not recommended.

**500 mg/125 mg film-coated tablets:**
Ask your doctor or pharmacist for advice when giving Co-amoxiclav tablets to children weighing less than 40 kg.

**Patients with kidney and liver problems**
If you have kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor.

If you have liver problems you may have more frequent blood tests to check how your liver is working.

**How to take Co-amoxiclav Tablets**
Swallow the tablets whole with a glass of water at the start of a meal or slightly before.

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 2 weeks. If you still feel unwell you should go back to see the doctor.

**If you take more Co-amoxiclav than you should**
If you take too much Co-amoxiclav, signs might include an upset stomach (feeling sick, being sick or diarrhoea) or convulsions. Talk to your doctor as soon as possible. Take the medicine carton or bottle to show the doctor.

**If you forget to take Co-amoxiclav**
If you forget to take a dose, take it as soon as you remember. You should not take the next dose too soon, but wait about 4 hours before taking the next dose.
If you stop taking Co-amoxiclav
Keep taking Co-amoxiclav until the treatment is finished, even if you feel better. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Co-amoxiclav can cause side effects, although not everybody gets them.

Conditions you need to look out for

Allergic reactions:
- skin rash
- inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body
- fever, joint pain, swollen glands in the neck, armpit or groin
- swelling, sometimes of the face or mouth (angioedema), causing difficulty in breathing
- collapse.

Warning: Allergic reactions can sometimes occur delayed.

Contact a doctor immediately if you get any of these symptoms. Stop taking Co-amoxiclav Tablets.

Inflammation of large intestine
Inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever.

Contact your doctor as soon as possible for advice if you get these symptoms.

Very common side effects
These may affect more than 1 in 10 people
- diarrhoea (in adults).

Common side effects
These may affect up to 1 in 10 people
- thrush (candida - a yeast infection of the vagina, mouth or skin folds)
- feeling sick (nausea), especially when taking high doses
- if affected take Co-amoxiclav before food
- vomiting.
- diarrhoea (in children)

Uncommon side effects
These may affect up to 1 in 100 people
- skin rash, itching
- raised itchy rash (hives)
- indigestion
- dizziness
- headache.

Uncommon side effects that may show up in your blood tests:
- increase in some substances (enzymes) produced by the liver

Rare side effects
These may affect up to 1 in 1000 people
- skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge-erythema multiforme

If you notice any of these symptoms contact a doctor urgently

Rare side effects that may show up in your blood tests:
- low number of cells involved in blood clotting
- low number of white blood cells.

Other side effects
Other side effects have occurred in a very small number of people but their exact frequency is unknown.
- Allergic reactions (see above)
- Inflammation of the large intestine (see above)
- Serious skin reactions:
  - a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form causing extensive peeling of the skin (more than 30% of the body surface toxic epidermal necrolysis)
  - widespread red skin rash with small pus-containing blisters (bullous exfoliative dermatitis)
  - a red, scaly rash with bumps under the skin and blisters (exanthemous pustulosis).

Contact a doctor immediately if you get any of these symptoms.
- inflammation of the liver (hepatitis)
- jaundice, caused by increases in the blood of bilirubin (a substance produced in the liver) which may make your skin and whites of eyes appear yellow
- inflammation of tubes in the kidney
- blood takes longer to clot
- hyperactivity
- convulsions (in people taking high doses of Co-amoxiclav or who have kidney problems)
- black tongue which looks hairy
- stained teeth (in children), usually removed by brushing.
Side effects that may show up in your blood or urine tests:
- severe reduction in the number of white blood cells
- low number of red blood cells (haemolytic anaemia)
- crystals in urine.

If you get side effects

Tell your doctor or pharmacist if any of the side effects become severe or troublesome, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE CO-AMOXICLAV TABLETS

Keep out of the reach and sight of children.

Do not store above 25°C.

Do not take Co-amoxiclav after the expiry date which is stated on the carton and blister strip after EXP. The expiry date refers to the last day of that month.

Do not take Co-amoxiclav Tablets if you notice any visible signs of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Co-amoxiclav contains:
- The active substances are Amoxicillin Trihydrate and Potassium Clavulanate Diluted.

250mg/125mg Tablets: Each film-coated tablet contains 250mg amoxicillin as amoxicillin trihydrate and 125mg of clavulanic acid as potassium clavulanate, diluted.

500mg/125mg Tablets: Each film-coated tablet contains 500mg amoxicillin as amoxicillin trihydrate and 125mg of clavulanic acid as potassium clavulanate, diluted.

- The other ingredients are:
  Cellulose, microcrystalline (E460)
  Sodium starch glycolate, Type A
  Silica, Colloidal anhydrous (E551)
  Magnesium Stearate (E572)

Film coat
- Titanium dioxide (E171)
- Hypromellose (E464)
- Polyethylene glycol

What Co-amoxiclav looks like and contents of the pack

250mg/125mg Tablets: White, capsule-shaped, film coated tablet debossed with '1 05' on one side and plain on the other.

500mg/125mg Tablets: White, capsule-shaped film-coated tablet, debossed with '1 06' on one side and plain on the other.

The tablets are packaged in aluminium blister strips consisting of: 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 20, 21, 25, 30, 35, 40, 50, 100 & 500 tablets

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
Brown & Burk UK Ltd
6 Marryn Close
Hounslow West
Middlesex
TW4 5DQ
UK.

This medicinal product is authorised in the Member States of the EEA under the following names:

UK & IE: Co-amoxiclav 250mg/125mg
Film-coated Tablets & Co-amoxiclav 500mg/125mg Film-coated Tablets

SE: Amoxicillin/Clavulanic acid BB 250mg/125mg filmdragerade tablett & Amoxicillin/Clavulanic acid BB 500mg/125mg filmdragerade tablett

This leaflet was last approved on 12/2011
Module 4
Labelling
<table>
<thead>
<tr>
<th>Amoxicillin/clavulanic acid</th>
<th>Brown &amp; Bark UK Ltd</th>
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<td>Co-amoxiclav 250mg/125mg</td>
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</tbody>
</table>
Co-amoxiclav 500mg/125mg Film-coated Tablets

Each film-coated tablet contains 500mg amoxicillin as amoxicillin trihydrate and 125mg of clavulanic acid as potassium clavulanate.

Contains Pregelatin.

Read the package leaflet before use.

Oral use.

Keep out of the reach and sight of children.

Store below 25°C.

Use as directed by the physician.
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Co-amoxiclav 250mg/125mg and 500mg/125mg Film-coated Tablets (PL 25298/0007-8; UK/H/3244/001-2/DC) could be approved. The products are prescription-only medicines for the treatment of the following bacterial infections in adults and children:

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

**Co-amoxiclav 500mg/125mg Film-coated Tablets**
- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Bone and joint infections, in particular osteomyelitis

These are applications made under the decentralised procedure (DCP), with the UK as RMS, and Ireland and Sweden as CMS. The applications were submitted according to Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products of Augmentin 375mg and 625mg Film-coated Tablets (Beecham Group plc), which were originally granted Marketing Authorisations in 1981 and 1991, respectively.

Amoxicillin is a member of the penicillin family. The penicillin nucleus consists of a thiazolidine ring connected to a β-lactam ring, to which a side-chain is attached. The side-chain determines most of the pharmacological and antibacterial properties of the penicillin in question. In the case of amoxicillin the benzyl ring in the side chain extends the range of antimicrobial activity into the Gram-negative bacteria. Amoxicillin kills bacteria by interfering with the synthesis of the bacterial cell wall. As a result the bacterial cell wall is weakened, the cell swells and then ruptures. Amoxicillin is readily hydrolysed by the staphylococcal penicillinase. Its spectrum of activity is extended by administration with the β-lactamase inhibitor clavulanic acid. Clavulanate by itself has little antibacterial activity.

No new non-clinical studies were conducted, which is acceptable given that the applications were generics of originator products which have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Co-amoxiclav 250mg/125mg Film-coated Tablets  
Co-amoxiclav 500mg/125mg Film-coated Tablets |
|-------------------------------------------------|------------------------------------------------------------------------------------------|
| Name(s) of the active substance(s) (INN)         | Amoxicillin triglydrate 
Potassium clavulanate                                                                    |
| Pharmacotherapeutic classification (ATC code)    | Beta-lactam antibacterials, penicillin 
(J01C R02)                                                                              |
| Pharmaceutical form and strength(s)             | 250mg/125mg Film-Coated Tablets  
500mg/125mg Film-Coated Tablets                                                           |
| Reference numbers for the Mutual Recognition Procedure | UK/H/3244/001-2/DC                                                                  |
| Reference Member State                          | United Kingdom                                                                         |
| Member States concerned                         | Ireland and Sweden                                                                     |
| Marketing Authorisation Number(s)               | PL 25298/0007-8                                                                        |
| Name and address of the authorisation holder     | Brown & Burk UK Ltd, 5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ, United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

ACTIVE SUBSTANCE – AMOXICILLIN TRIHYDRATE

INN:  Amoxicillin trihydrate

Chemical Name:  \((2S,5R,6R)-6-[(R)-(\sim)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate\) 

7-[2-amino-2-(4-hydroxyphenyl) -acetyl]amino-3,3-dimethyl-6-oxo -2-thia-5-azabicyclo[3.2.0] heptane -4-carboxylic acid

Molecular Formula:  \(\text{C}_{16}\text{H}_{19}\text{N}_{3}\text{O}_{5}\text{S} \cdot 3\text{H}_{2}\text{O}\)

Appearance:  A white or almost white, crystalline powder, slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils, chloroform and ether. 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 a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

ACTIVE SUBSTANCE – POTASSIUM CLAVULANATE

INN:  Potassium clavulanate

Chemical Name:  \((Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate\)

Molecular Formula:  \(\text{C}_{8}\text{H}_{8}\text{KNO}_{5}\)

Appearance:  A white or almost white, crystalline, hygroscopic powder, freely soluble in water, slightly soluble in alcohol and 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 a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose (E460), sodium starch glycolate (Type A), colloidal anhydrous silica (E551), magnesium stearate (E572), titanium dioxide (E171), hypromellose (E464) and polyethylene glycol.

All excipients are controlled to their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients is sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate stable, efficacious and tolerable film-coated tablets containing amoxicillin trihydrate and potassium clavulanate that can be considered generic medicinal products of Augmentin 375mg and 625mg Film-coated Tablets (Beecham Group plc).

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.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

Both strengths of tablets are packaged in aluminium blister strips, which are then enclosed in a cardboard box. Pack sizes for both strengths are 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 20, 21, 25, 30, 35, 40, 50, 100 and 500 film-coated tablets. Not all pack sizes are to be marketed.

However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the storage conditions ‘Do not store above 25°C’.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of amoxicillin trihydrate and potassium clavulanate are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical overview is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are
already marketed, no increase in environmental burden is anticipated.

The grant of Marketing Authorisations is recommended from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

**An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Co-amoxiclav 500mg/125mg Film-coated Tablets versus the reference product Augmentin 625mg Tablets (Beecham Group plc, UK) in healthy male volunteers under fasted conditions.**

Volunteers were dosed with either treatment. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results are presented below:

**Amoxicillin (based on geometric means)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (T)</th>
<th>Reference (R)</th>
<th>% Ratio T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>7734.46</td>
<td>7269.43</td>
<td>106.39</td>
<td>98.06-115.44</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>24651.87</td>
<td>23510.96</td>
<td>104.85</td>
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<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>25152.51</td>
<td>24019.26</td>
<td>104.71</td>
<td>97.61-112.34</td>
</tr>
</tbody>
</table>

**Clavulanic Acid (based on geometric means)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (T)</th>
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</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>2744.60</td>
<td>2726.76</td>
<td>100.65</td>
<td>88.36-114.65</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>6266.60</td>
<td>6315.38</td>
<td>99.22</td>
<td>88.12-111.72</td>
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<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>6490.39</td>
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The test and reference products are within conventional 90% confidence intervals of 80-125% for amoxicillin and clavulanic acid. In conclusion, bioequivalence has been shown between the test and reference products.

**An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Co-amoxiclav 250mg/125mg Film-coated Tablets versus the reference product Augmentin 375mg Tablets (Beecham Group plc, UK) in healthy male volunteers under fasted conditions.**

Volunteers were dosed with either treatment. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results are presented below:

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<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>3939.22</td>
<td>4231.30</td>
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<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>12576.86</td>
<td>13214.18</td>
<td>95.18</td>
<td>90.77-99.80</td>
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**Clavulanic Acid (based on geometric means)**

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The test and reference products are within conventional 90% confidence intervals of 80-125% for amoxicillin and clavulanic acid. In conclusion, bioequivalence has been shown between the test and reference products.

**Efficacy**
No new data on the efficacy of either active substance are submitted and none are required for these types of applications.

**Safety**
No new or unexpected safety issues were raised by the bioequivalence data.

**SmPC, PIL, Labelling**
The SmPCs, PIL and labelling are medically acceptable. The SmPCs are consistent with those for the originator products.

**Conclusion**
The grant of Marketing Authorisations is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Co-amoxiclav 250mg/125mg and 500mg/125mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted and none are required for applications of this type.

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Co-amoxiclav 250mg/125mg and 500mg/125mg Film-coated Tablets and their respective originator products.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the originator products.

**RISK-BENEFIT ASSESSMENT**
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. 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.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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