1.3 PRODUCT INFORMATION

1.3.1 Summary of the product characteristics (SMPC)

Name of the product: Co-Amoxiclav tablets 375 mg

Qualitative and quantitative composition:

Amoxicillin Trihydrate BP eq. to Amoxicillin	250 mg
Diluted Potassium Clavulanate BP eq. to Clavulanic Acid	125 mg
Excipients	Q.S
Colour: Titanium Dioxide BP	

4.1 Therapeutic indications

Co-Amoxiclav is indicated for the treatment of the following infections in adults and children

- Acute bacterial sinusitis (properly 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 in terms of amoxicillin/clavulanic acid content, except when doses are stated in terms of the individual components.

The dose of Co-Amoxiclav used to treat an individual infection should take into account:

- The expected pathogens and it/ their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection being treated.
- The age, weight and renal function of the patient are shown below.

Alternative presentations of Co-Amoxiclav (e.g. those used to 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).

Adults and children ≥ 40 kg): this formulation of Co-Amoxiclav tablet BP 250/125mg gives a maximum dose of 750 mg amoxicillin and 375 mg clavulanic acid when given as recommended below. If a higher daily dose of amoxicillin is required, it is recommended that another preparation of Co-Amoxiclav is used 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.

Dosage in Dental Infections: (e.g. dentalveolar abscess) one Co-Amoxiclav tablet 3 times a day for 5 days.

Adults and children ≥40 kg

One 250 mg/125 mg tablet to be 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 adjustment to the dose is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended levels of amoxicillin.

No adjustment in the dose is required in patients with creatinine clearance CrCl) greater than 30 ml/min.

Adults and children ≥40 kg

CrCl: 10-30 ml/min	250 mg/125 mg twice daily
CrCl < 10 ml /min	250 mg/125 mg once daily
Haemodialysis	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)

Children < 40 kg

In children < 40 kg with a creatinine clearance of less than 30 ml/min, using Co-amoxiclav presentations with an amoxicillin to clavulanic acid ratio of 2:1 is not recommended, as no dose adjustments are available. In these 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 .

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 reactions (including anaphylactoid and severe cutaneous adverse 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 feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires discontinuation of Co-Amoxiclav 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 contraindicated 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.

Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal 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 foetal 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 the benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects of 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.

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 are 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	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon

Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known

Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[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 amoxicillin/clavulanic acid at the start of a meal.

[4] Including pseudomembranous colitis and haemorrhagic colitis

[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 .

[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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 lyses and cell 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 in Co-Amoxiclav are:

- the inactivation by bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- alteration of the PBPs, which reduce the affinity of the antibacterial agent for the target.

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

Breakpoints

MIC breakpoints for Co-Amoxiclav are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤1	-	> 1
Moraxella catarrhalis[1]	≤1	-	> 1
Staphylococcus aureus [2]	≤2	-	> 2
Coagulase-negative staphylococci [2]	≤0.25		> 0.25
Enterococcus[1]	≤4	8	> 8
Streptococcus A, B, C, G[5]	≤0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤4	8	> 8
Gram-positive Anaerobes[1]	≤4	8	> 8
Non-species related breakpoints[1]	≤2	4-8	> 8

[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)£
Streptococcus agalactiae
Streptococcus pneumoniae[1]
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
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £All methicillin-resistant staphylococci are resistant to Co-Amoxiclav. [1] *Streptococcus pneumoniae* that is fully susceptible to penicillin may be treated with this presentation of Co-Amoxiclav. Organisms that show any degree of reduced susceptibility to penicillin should not be treated with this presentation (see sections 4.2 and 4.4). [2] 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 an aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral administration. Absorption of Co-Amoxiclav is optimised when taken at the start of a meal. Following oral administration, Co-Amoxiclav are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

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

Mean (± SD) pharmacokinetic parameters

Active substance(s) administered	Dose	C_{max}	T_{max} *	AUC (0-24h)	T 1/2
	(mg)	(µg/ml)	(h)	((µg.h/ml)	(h)
Amoxicillin					
AMX/CA 250 mg/125 mg	250	3.3 ± 1.12	1.5 (1.0-2.0)	26.7±4.56	1.36 ± 0.56
Clavulanic acid					
AMX/CA 250 mg/125 mg	125	1.5 ± 0.70	1.2 (1.0-2.0)	12.6 ± 3.25	1.01 ± 0.11

AMX – amoxicillin, CA – clavulanic acid

* Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with Co-Amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid on their own.

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 0.2 l/kg for the clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in the 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, as with trace quantities of clavulanic acid (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 of 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 eliminated by both renal and non-renal mechanisms.

Co-Amoxiclav has a mean elimination half-life of around an 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 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 Co-Amoxiclav to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or the clavulanic acid.

Renal impairment

The total serum clearance of Co-Amoxiclav decreases proportionately along with decreasing renal function. The reduction in the 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 impairmen. 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 their liver function monitored at regular intervals.

5.3 Preclinical safety data

Non-clinical data revealed that Co-Amoxiclav causes no special hazard to humans based on studies from safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with Co-Amoxiclav demonstrated gastric irritancy and vomiting, and discolouring of the tongue.

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

1.3.2 Labelling (outer & inner label)

Please find the enclosed attachment.

1.3.3 Package Insert

Please find the enclosed attachment.

1.4 Regional Summaries

1.4.1 Bioequivalence trial information Form

1.4.2 Quality Information Summary (QIS)

1.5 Electronic Review Documents

1.6 Samples

Please find the enclosed attachment.