Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 500 mg/100 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg amoxicillin (as amoxicillin sodium) and 100 mg clavulanic acid (as clavulanate potassium)

Each vial contains 1.4 mmol (31.4 mg) of sodium
Each vial contains 0.5 mmol (19.6 mg) of potassium

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion
White powder

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):

-severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
-acute exacerbations of chronic bronchitis (adequately diagnosed)
-community acquired pneumonia
-cystitis
-pyelonephritis
-skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis
-bone and joint infections, in particular osteomyelitis
-intra-abdominal infections
-female genital infections

Prophylaxis against infections associated with major surgical procedures in adults, such as those involving the:
-gastrointestinal tract
-pelvic cavity
-head and neck
-biliary tract surgery

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

4.2 Posology and method of administration

Posology
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 amoxicillin/ clavulanic acid 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).

This powder for solution for injection/infusion provides a total daily dose of 3000 mg amoxicillin and 600 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 an alternative intravenous formulation of amoxicillin/ clavulanic acid is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

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).

Consideration should be given to local guidelines on appropriate dosing frequencies for amoxicillin/clavulanic acid.

Adults and children ≥ 40 kg

For treatment of infections as indicated in section 4.1: amoxicillin /clavulanic acid 1000 mg/200 mg every 8 hours

For surgical prophylaxis	For procedures less than 1 hour in duration, the recommended dose of amoxicillin/ clavulanic acid is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia (doses of 2000 mg/200 mg can be achieved by using an alternative intravenous formulation of amoxicillin/clavulanic acid). For procedures greater than 1 hour in duration, the recommended dose of amoxicillin/ clavulanic acid is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia, with up to 3 doses of 1000 mg/200 mg in 24 hours. Clear clinical signs of infection at operation will require a normal course of intravenous or oral therapy post-operatively.

Children < 40 kg

Recommended doses:

-*Children aged 3 months and over:* 25 mg/5 mg per kg every 8 hours
-*Children aged less than 3 months or weighing less than 4 kg:* 25 mg/5 mg per kg every 12 hours

Elderly

No dose adjustment is considered necessary.

Renal impairment

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

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given twice daily
CrCl < 10 ml /min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given every 24 hours
Haemodialysis	Initial dose of 1000 mg/200 mg and then followed by 500 mg/100 mg every 24 hours, plus a dose of 500 mg/100 mg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10 to 30 ml/min	25 mg/5 mg per kg given every 12 hours
CrCl < 10 ml /min	25 mg/5 mg per kg given every 24 hours
Haemodialysis	25 mg/5 mg per kg given every 24 hours, plus a dose of 12.5 mg/2.5 mg per kg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

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 intravenous use.

Co-amoxiclav may be administered either by slow intravenous injection over a period of 3 to 4 minutes directly into a vein or via a drip tube or by infusion over 30 to 40 minutes. Co-amoxiclav is not suitable for intramuscular administration.

Children aged less than 3 months should be administered Co-amoxiclav by infusion only.

Treatment with amoxicillin/clavulanic acid may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

-Hypersensitivity to the active substances or to penicillins
-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 reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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 amoxicillin/clavulanic acid may not be suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. As no specific data for T>MIC are available and the data for comparable oral presentations are borderline, this presentation (without additional amoxicillin) may not be suitable for the treatment of 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 contraindicates 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 including amoxicillin 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 sections 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 (including acute renal injury) 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 4.8 and 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.

500 mg/100 mg powder for solution for injection or infusion
This medicinal product contains 31.4 mg sodium per vial, equivalent to 1.57% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

500 mg/100 mg powder for solution for injection or infusion
This medicinal product contains 19.6 mg (0.5 mmol) of potassium per vial. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

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 (MPA) 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.

Breast-feeding
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. Co-amoxiclav 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 amoxicillin/clavulanic acid, 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)

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Mucocutaneous candidosis
	Not known	Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders	Rare	Reversible leucopenia (including neutropenia) Thrombocytopenia
	Not known	Reversible agranulocytosis Haemolytic anaemia

		Prolongation of bleeding time and prothrombin time[1]
Immune system disorders[10]	Not known	Angioneurotic oedema Anaphylaxis Serum sickness-like syndrome Hypersensitivity vasculitis
Nervous system disorders	Uncommon	Dizziness Headache
	Not known	Convulsions[2] Aseptic meningitis
Vascular disorders	Rare	Thrombophlebitis[3]
Cardiac disorders	Not known	Kounis syndrome
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Nausea Vomiting Indigestion
	Not known	Antibiotic associated colitis[4] Drug-induced enterocolitis syndrome Pancreatitis acute
Hepatobiliary disorders	Uncommon	Rises in AST and/or ALT[5]
	Not known	Hepatitis[6] Cholestatic jaundice[6]
Skin and subcutaneous tissue disorders[7]	Uncommon	Skin rash Pruritus Urticaria
	Rare	Erythema multiforme
	Not known	Stevens-Johnson syndrome Toxic epidermal necrolysis Bullous exfoliative-dermatitis Acute generalised exanthemous pustulosis (AGEP)[9] Drug reaction with eosinophilia and systemic symptoms (DRESS) Linear IgA disease
Renal and urinary disorders	Not known	Interstitial nephritis Crystalluria[8] (including acute renal injury)

[1] See section 4.4
[2] See section 4.4
[3] At the site of injection
[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

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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: Antibacterials for systemic use; Combinations of penicillins, incl. beta-lactamase inhibitors
ATC code: J01CR02

Mechanism 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.

Pharmacokinetic/pharmacodynamic 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)

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for amoxicillin/clavulanic acid and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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[1]
Streptococcus pyogenes and other beta-haemolytic streptococci
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Actinobacillus actinomycetemcomitans
Capnocytophaga spp.
Eikenella corrodens
Haemophilus influenzae[2]
Moraxella catarrhalis
Neisseria gonorrhoeae§
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.
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas sp.
Serratia sp.
Stenotrophomonas maltophilia

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

$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid.
§ All strains with resistance to amoxicillin that is not mediated by beta-lactamases are resistant to amoxicillin/clavulanic acid.
[1] This presentation of amoxicillin/clavulanic acid may not be suitable for treatment of *Streptococcus pneumoniae* that are resistant to penicillin (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
The pharmacokinetic results for studies in which amoxicillin/clavulanic acid was administered to groups of healthy volunteers as either 500 mg/100 mg or 1000 mg/200 mg given as a bolus intravenous injection are presented below.

Mean (± SD) pharmacokinetic parameters

Bolus intravenous injection

Dose administered	**Amoxicillin**				
	Dose	Mean peak serum conc. (microg/ml)	T 1/2 (h)	AUC (h.mg/l)	Urinary recovery (%, 0 to 6 h)
AMX/CA 500 mg/100 mg	500 mg	32.2	1.07	25.5	66.5
AMX/CA 1000 mg/200 mg	1000 mg	105.4	0.9	76.3	77.4
Clavulanic acid					
AMX/CA 500 mg/100 mg	100 mg	10.5	1.12	9.2	46.0
AMX/CA 1000 mg/200 mg	200 mg	28.5	0.9	27.9	63.8

AMX – amoxicillin, CA – clavulanic acid

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 a single 500/100 mg or a single 1000/200 mg bolus intravenous injection. 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.

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

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Co-amoxiclav should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions. If prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Co-amoxiclav solutions should not be mixed with infusion solutions containing glucose, dextran or bicarbonate.

6.3 Shelf life

2 years

Shelf-life after dilution or reconstitution

Reconstituted vials (for intravenous injection or before dilution for infusion)
The reconstituted solution (one 500mg/100mg vial in 10mL of water for injection) should be used immediately, i.e. within 15 minutes, or further diluted for intravenous infusion.

Reconstituted and diluted solution (for intravenous infusion)
Chemical and physical in-use stability has been demonstrated after reconstitution and further dilution to 50 mL (500 mg/100 mg) as shown in the following table:

Infusion Fluid	**Solution storage temperature**	
	5°C	**25°C**
WFI	1h	1h
Sodium Chloride intravenous infusion 0.9%	1h	1h
Ringer Solution	-	1h
Hartmann's Solution; Ringer-Lactate Solution	-	1h
Potassium Chloride 0.3% - Sodium Chloride 0.9% solution for infusion	-	1h

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used, immediately, in-use storage times and conditions are the responsibility of the user and would not be longer than the times stated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

Do not store above 25°C

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Clear glass vial (Ph.Eur. Type III) fitted with a chlorobutyl rubber stopper and an aluminium ring.

Pack sizes: 1 or 10 vials in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any unused solution should be discarded.
Reconstitution/dilution must be performed under aseptic conditions. The solution must be visually inspected for particulates and discolouration prior to administration. The solution should only be used if it is clear and free of particles.
Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of solutions for intravenous injection
Water for Injection Ph. Eur. is the normal solvent.
Co-amoxiclav 500 mg/100 mg should be dissolved in 10 ml of solvent. This yields approximately 10.2 ml of solution for single-dose use.

A transient pink colouration may or may not develop during reconstitution.

Reconstituted solutions are normally colourless or a pale straw colour.

Co-amoxiclav should be administered immediately.

Preparation of solutions for intravenous infusion
Co-amoxiclav vials are not suitable for multi-dose use.

Co-amoxiclav 500 mg/100 mg should be reconstituted as described above for injection. Without delay the reconstituted solution should be diluted to at least 50 ml of infusion fluid using a minibag or in-line burette.

Intravenous infusions of Co-amoxiclav may be administered with the following infusion fluids.

Compatible diluents
Water for injections Ph.Eur.
Sodium chloride 9 mg/ml (0.9%) solution for infusion
Ringers Solution
Hartmann's Solution; Ringer-Lactate Solution
Potassium chloride and Sodium chloride solution for infusion

Sufficient antibiotic concentrations are obtained at room temperature (25° C) in the recommended volume of the above infusion fluids for the times stated in section 6.3. After reconstitution, dilution and storage at room temperature (25° C), infusions should be completed within the time indicated in the table in section 6.3.

The stability of Co-amoxiclav solutions for intravenous use is concentration-dependent. If more concentrated solutions are required, the stability periods should be adjusted accordingly.

Co-amoxiclav for intravenous use is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solutions of Co-amoxiclav should therefore not be premixed with such infusions, but can be injected into the infusion tube over a period of 3 to 4 minutes.

7 MARKETING AUTHORISATION HOLDER

Instituto Biochimico Italiano G. Lorenzini S.p.A.
Via Fossignano, 2
04011 Aprilia (LT)
Italy

8 MARKETING AUTHORISATION NUMBER

PA2220/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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