



**National Agency for Food & Drug Administration &
Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R)
Directorate**

**SUMMARY OF PRODUCT CHARACTERISTICS
(SmPC) MAXICLAV INJECTION**

1. NAME OF THE MEDICINAL PRODUCT

(MAXICLAV INJECTION) Co-amoxiclav for Injection BP 1.2g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Combi pack contains:

Each vial contains

Sterile Amoxicillin Sodium BP

Equivalent to Amoxicillin 1g

Sterile Potassium Clavulanate BP

Equivalent to Clavulanic acid 200mg

Sterile Water for Injection USP 20ml

3. PHARMACEUTICAL FORM

Dry powder for injection; almost white to off white powder

4. Clinical particulars

4.1 Therapeutic indications

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

- 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 the 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 Co-amoxiclav that is selected to treat an individual infection should consider:

- 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)

This Co-amoxiclav powder for solution for injection or infusion provides a total daily dose of 3000mg amoxicillin and 600mg 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 Co-amoxiclav is selected 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 \geq 40kg

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

For surgical prophylaxis	<p>For procedures less than 1 hour in duration, the recommended dose of Co-amoxiclav is 1000 mg/200mg 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 Co-amoxiclav).</p> <p>For procedures greater than 1 hour in duration, the recommended dose of Co-amoxiclav is 1000 mg/200mg to 2000 mg/200 mg given at induction of anaesthesia, with up to 3 doses of 1000 mg/200 mg in 24 hours.</p> <p>Clear clinical signs of infection post at operation will require a normal course of intravenous or oral therapy post-operatively.</p>
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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 12hours.

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 30ml/min

Adults and children \geq 40kg

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 <40kg

CrCl: 10-30 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 min directly into a vein or via a drip tube or by infusion over 30 to 40 min. Co-amoxiclav is not suitable for intramuscular administration.

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

Treatment with Co-amoxiclav may be initiated using an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient. For instructions on reconstitution of the product see section 6.6.

4.3 Contraindications

Co-amoxiclav is contraindicated - in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins - in patients with a previous history of amoxicillin clavulanate-associated jaundice/hepatic dysfunction.

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 betalactam agents (see section 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. 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 should 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 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 betalactamases 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 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.

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 normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

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. A change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 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.

Breastfeeding

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.

4.8 Undesirable effects

The most 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)

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	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon

4.9 Overdose

Signs and Symptoms

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. 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.

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

5.2 Pharmacodynamics properties

Pharmacotherapeutic Group: Combinations of penicillins, incl. beta-lactamase inhibitors
ATC code: J01CR02

Mechanism of Action

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
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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, G5	≤ 0.25	-	> 0.25

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

Gardnerella vaginalis

Staphylococcus aureus (methicillin-susceptible)[£]

Streptococcus agalactiae

Streptococcus pneumoniae¹

Streptococcus pyogenes and other beta-haemolytic streptococci

Streptococcus viridans group

Aerobic Gram-negative micro-organisms

Actinobacillus actinomycetemcomitans

Capnocytophaga 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

5.3 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.

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.

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.

5.4 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 None

6.2 Incompatibilities

Co-amoxiclav Injection should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions. Co-amoxiclav Injection should not be mixed with infusions containing glucose, dextran or bicarbonate (see section 4.2 for more information). If co-amoxiclav is prescribed concurrently 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.

6.3 Shelf life

Unopened-2 years

Use the reconstituted solution immediately. Discard any unused solution

6.4 Special precautions for storage

Store in a cool and dry place below 25°C, protect from light

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

Co-Amoxiclav for injection is supplied in 20 ml Glass vial USP Type-I closed with bromo butyl rubber stopper, sealed with Al, Flip off Seal.

6.6 Special precautions for disposal <and other handling>

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 APPLICANT

Evans Baroque Nigeria Limited
Km 32, Lagos – Badagry Expressway,
Agbara Industrial Estate, Agbara,
Ogun State, Nigeria
08033304149

info@evansbaroque.com

MANUFACTURER

Inject Care Parenterals Pvt. Ltd
Plot no. 130, Silvassa Road,
G.ID. C. Vapi-396195, Gujarat,
India
+91-6359299966, 8511149413

contact@injectcare.com