Summary Product Characteristics (SPC)

Product information for Health Professionals (For All Products subject to Medical Prescription)

1. Name of the medicinal product

HUAXICLA 1000mg/200mg (Co-amoxiclav) Powder for Solution for Injection

2. Qualitative and quantitative composition

Each vial contains sterile white or almost white powder providing potassium clavulanate equivalent to 200mg clavulanic acid with amoxicillin sodium equivalent to 1g amoxicillin.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile powder for injection

A white or almost white powder supplied in 25ml tubular glass vial stoppered with butyl rubber stopper and capped with flip-off cap.

4. Clinical particulars

4.1 Therapeutic indications

Co-amoxiclav for injection should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Co-amoxiclav for injection is indicated for the short term treatment of common bacterial infections such as:

Upper Respiratory Tract Infections (including ENT): e.g. tonsillitis, sinusitis, otitis media

Lower Respiratory Tract Infections: e.g. acute exacerbations of chronic bronchitis, lobar and broncho-pneumonia

Genito-urinary Tract Infections: e.g. cystitis, urethritis, pyelonephritis, female genital infections

Skin and Soft Tissue Infections

Bone and Joint Infections: e.g. osteomyelitis

Other Infections: e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis, septicaemia, peritonitis, post-surgical infections.

Co-amoxiclav for injection is indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and

biliary tract surgery.

Susceptibility to Co-amoxiclav for injection will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Infections caused by amoxicillin susceptible organisms are amenable to Co-amoxiclav for injection treatment due to its amoxicillin content. Mixed infections caused by amoxicillin susceptible organism in conjunction with Co-amoxiclav for injection -susceptible beta-lactamase-producing organisms may therefore be treated by Co-amoxiclav for injection.

4.2 Posology and method administration

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

Posology

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.

Co-amoxiclav for injection may be administered either by IV injection or by intermittent infusion.

Treatment should not exceed 14 days without re-evaluation of the patient.

Usual Recommended IV Co-amoxiclav Dose：

Adults and Children 12 yrs and older (> 40 kg)	1.2 g (Amoxicillin 1000 mg + Clavulanic acid 200 mg) every 6 to 8 hrs, depending on the severity of infection
Children 3 mos to 12 yrs old	30 mg (Amoxicillin 25 mg + Clavulanic acid 5 mg) per kg BW 6 to 8 hrs, depending on the severity of infection.
Children 0 to 3 mos (> 4 kg)	30 mg (Amoxicillin 25 mg + Clavulanic acid 5 mg) per kg BW every 8 hrs
Children 0 to 3 mos (< 4 kg)	30 mg/kg(Amoxicillin 25 mg +

	Clavulanic acid 5 mg) per kg BW every 12 hrs
Or, as prescribed by a physician.	

Dosage for Surgical Prophylaxis:

Surgical prophylaxis with Co-amoxiclav should aim to protect the patient for the period of risk of infection.

- In adults, procedures lasting less than one (1) hr are successfully covered by IV Co-amoxiclav 1.2 g (Amoxicillin 1000 mg + Clavulanic acid 200 mg) administered at induction of anesthesia.
- Longer operations or when there is a high risk of infection (e.g., colorectal surgery) may require subsequent doses of IV Co-amoxiclav 1.2 g (Amoxicillin 1000 mg + Clavulanic acid 200 mg) [up to 4 doses in 24 hrs], and this regimen can be continued for several days if the procedure has significantly increased the risk of infection.
- Clear clinical signs of infection at operation will require a normal course of IV or oral Co-amoxiclav therapy post-operatively.

Dosage in Elderly Patients:

No dosage adjustment necessary. However, if there is evidence of renal impairment, dose should be adjusted as for renally- impaired adults.

Dosage in Patients with Renal Impairment:

Dosing adjustments are based on the maximum recommended level of amoxicillin.

Renal Impairment	**Recommended IV Co-amoxiclav Dose in Renal Impairment**	
	Adults	**Children**
Mild Impairment (CL_{CR} >30 mL/min)	No dosage adjustment necessary	No dosage adjustment necessary
Moderate Impairment (CL_{CR} 10 to 30 mL/min	1.2 g* (Amoxicillin 1000 mg + Clavulanic acid 200 mg) IV stat followed by 600 mg (Amoxicillin 500 mg + Clavulanic acid 100 mg) IV every 12 hrs	30 mg (Amoxicillin 25 mg + Clavulanic acid 5 mg) per kg body weight every 12 hrs
Severe Impairment (CL_{CR} <10 mL/min)	· 1.2 g*(Amoxicillin 1000 mg + Clavulanic acid 200 mg) IV stat followed by 600 mg (Amoxicillin 500 mg + Clavulanic acid 100 mg) IV every 24 hrs. · An additional 600 mg	· 30 mg (Amoxicillin 25 mg + Clavulanic acid 5 mg) per kg BW every 24 hrs · An additional 15

	(Amoxicillin 500 mg + Clavulanic acid 100 mg) IV dose may need to be supplemented at the end of dialysis.**	mg (Amoxicillin 12.5 mg + Clavulanic acid 2.5 mg) per kg BW may need to be supplemented at the end of dialysis.**

*Each 1.2 g vial of Co-amoxiclav contains about 1 mmol potassium and 3.1 mmol sodium

**Dialysis decreases serum concentrations of Co-amoxiclav.

Dosage in Patients with Hepatic Impairment:

Dose with caution; monitor hepatic function at regular intervals for both adults and children. Data on where to base the dosage recommendation have not been established.

Directions for Use

Directions for Reconstitution:

To reconstitute, dissolve IV Co-amoxiclav powder in the required amount of diluent (Water for Injection is the usual diluent). Reconstituted solutions are normally clear and colorless and free from foreign particles.

Co-amoxiclav Vial	Volume of Diluent (mL)
1.2 g (1000 mg/200 mg)	20

There are two ways of administering IV Co-amoxiclav:

- Slow IV Injection for 3 to 4 mins after reconstitution.
- IV Infusion over 30 to 40 mins (should be further diluted after reconstitution).

Preparation of IV Infusion:

Add without delay (i.e., Solutions should be made up to full infusion volume immediately after reconstitution), Co-amoxiclav 1.2 g (1000 mg/200 mg) reconstituted solution to 100 mL of 0.9%Sodium Chloride Injection. Infuse over 30 to 40 mins and complete within the time stated.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

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 organism(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 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, Co-amoxiclav 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 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 sections 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.

Sodium content

This medicinal product contains sodium in consideration of the WHO recommended maximum daily intake of 2g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

Potassium content

This medicinal product contains potassium. 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 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.

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 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. 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 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)

)RA System n Class	**non 100 to < 1/10)**	**mmon 1,000 to < 0)**	**10,000 to <1/1,000)**	**uency not known ot be estimated from able data)**
tions and tations	cutaneous dosis			growth of non-susceptible isms
l and lymphatic m disorders			sible leucopenia ding neutropenia), nbocytopenia	sible agranulocytosis, olytic anaemia,

				ngation of bleeding time rothrombin time[1]
une system ders[10]				neurotic oedema, hylaxis, n sickness-like ome, Hypersensitivity litis
ous system ders		ness ache		ulsions[2] ic meningitis
ac disorders				is syndrome
ular disorders			nbophlebitis[3]	
ointestinal ders	hoea	ea ting estion		iotic-associated colitis[4] -induced enterocolitis ome reatitits acute
tobiliary ders		in AST or ALT[5]		itis[6] static jaundice[6]
and taneous tissue ders[7]		rash tus aria	ema multiforme	ns-Johnson syndrome epidermal necrolysis us exfoliative-dermatitis generalised hemous pustulosis P)[9] reaction with ophilia and systemic toms (DRESS) r IgA disease
l and urinary ders				titial nephritis alluria(including acute injury)[8]

section 4.4
section 4.4
ıe site of injection
uding pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
oderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class otics, but the significance of these findings is unknown.
se events have been noted with other penicillins and cephalosporins (see section 4.4).
ıy hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
section 4.9
section 4.4
sections 4.3 and 4.4

Reporting of suspected adverse reactions:
Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

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

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)

Organism	**Susceptibility Breakpoints (mg/L)**	
	Susceptible	**Resistant**
Haemophilus influenzae	≤ 2[1]	> 2[1]
Moraxella catarrhalis	≤ 1[1]	> 1[1]

Staphylococcus spp.	Note[2,3]	Note[2,3]
Enterococcus spp.[4]	≤ 4[1,5]	> 8[1,5]
Streptococcus groups A, B, C, G[6]	Note[7]	Note[7]
Streptococcus pneumoniae[8]	Note[9,10]	Note[9,10]
Viridans group streptococci	Note[11]	Note[11]
Enterobacterales[12] (uncomplicated UTI only)	< 8[1] (< 32) [1]	> 8[1] (> 32)[1]
Gram-negative anaerobes	≤ 4[1]	> 8[1]
Gram-positive anaerobes	≤ 4 [1]	> 8[1]
Pasteurella multocida	≤ 1[1]	> 1[1]
Burkholderia pseudomallei	≤ 0.001[1]	> 8[1]
Non-species related breakpoints	≤ 2 [1]	> 8 [1]

[1] For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.

[2] Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β -lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins.

3Ampicillin susceptible S. saprophyticus are mecA-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

4Aminopenicillin breakpoints in enterococci are based on intravenous administration. Oral administration is relevant for urinary tract infections only.

5Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in E. faecalis (confirm with MIC) but common in E. faecium.

6 Streptococcus groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.

7 The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins

for streptococcus group B.

[8] *Streptococcus pneumoniae* do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.

[9]The oxacillin 1 µ g disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥ 20 mm, or benzylpenicillin MIC ≤ 0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, can be reported susceptible without further testing, except for cefaclor.

[10] Susceptibility inferred from ampicillin (MIC or zone diameter).

[11]For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.

[12]Aminopenicillin breakpoints in *Enterobacterales* are based on intravenous administration. Breakpoints for oral administration are relevant for uncomplicated urinary tract infections only. Breakpoints for other infections are under review.

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 microorganisms

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 microorganisms

Actinobacillus actinomycetemcomitans

Capnocytophaga spp.

Eikenella corrodens

Haemophilus influenzae[2]

Moraxella catarrhalis

Neisseria gonorrhoeae[§]

Pasteurella multocida

Anaerobic microorganisms

Bacteroides fragilis

Fusobacterium nucleatum

Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

Enterococcus faecium[$]

Aerobic Gram-negative microorganisms

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* **Other microorganisms** *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 (µ g/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					

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of 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).

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 mg/100 mg or a single 1000 mg/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).

Paediatric population

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.

Older people

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

Co-amoxiclav must not be mixed with amino acid solutions, lipid emulsions, blood and glucose solutions.

Co-amoxiclav is less stable in infusions containing dextran or bicarbonate. Reconstituted solution should, therefore, not be added to such infusions but may be injected into the drip tubing over a period of three to four minutes.

Because of the inactivation of aminoglycosides by amoxicillin, ***in-vitro*** mixing should be avoided.

6.3 Shelf life

3 years

Reconstituted product should be used immediately.

6.4 Special precautions for storage

Do not store above 30ºC. Store in original package.

KEEP OUT OF REACH OF CHILDREN

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the injection and infusion solutions should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.5 Nature and contents of container

Clear glass vials, stoppered with butyl rubber stopper and capped with aluminum-plastic cap. 1 vial per box, 10 vials per bigger box.

6.6 Special precautions for disposal and other handling

After contact with skin, wash immediately with water. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice if discomfort persists.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
North China Pharmaceutical Co., Ltd.

No.388, Heping East Road, Shijiazhuang,

Hebei, P.R. China.

Manufacturing site address:
North China Pharmaceutical Co., Ltd.

No.388, Heping East Road, Shijiazhuang,

Hebei, P.R. China.

8. Marketing authorization number

H2024/CTD9148/16249

9. Date of first registration

09/02/2024

10. Date of revision of the text:

05/11/2024