CO-AMOXICLAV

BACTIV

457 mg per 5 mL

P owder for Oral Suspension

ANTIBACTERIAL (PENICILLIN)

FORMULATION

Each 5 mL of the reconstituted suspension contains:
Amoxicillin (as Trihydrate)..... 400 mg
Clavulanic Acid (as Potassium Clavulanate)..... 57 mg

PHARMACEUTICAL FORM

Powder for oral suspension: off-white powder

CLINICAL PARTICULARS

Therapeutic indications

Treatment of bacterial infections induced by Gram-negative and Gram-positive amoxicillin resistant microorganisms whose resistance is caused by β-lactamases which however are sensitive to the combination of amoxicillin and clavulanic acid.

Amoxicillin/clavulanic acid powder for oral suspension is suitable for treatment of the following indications when or likely to be due to susceptible organisms (see pharmacodynamics properties)

- Infections of the upper respiratory tract (including ear-nose-throat), in particular sinusitis, otitis media, recurrent tonsillitis
- Infections of the lower respiratory tract, in particular acute exacerbations of chronic bronchitis and bronchopneumonia
- Genital and urinary tract infections
- Infections of the skin and soft tissues

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

DOSAGE AND METHOD OF ADMINISTRATION

The dosage of amoxicillin/clavulanic acid powder for oral suspension depends on the age, weight and renal function of the particular patient, on the severity and the site of the infection and on the suspected or demonstrated causative agents.

The single dose should be taken at regular intervals throughout the day ideally at 12 hour intervals.
Usual recommended daily dosage for children aged two months to 12 years

- 25/3.6 mg/kg/day in mild to moderate infections (skin and soft tissue infections)
- 45/6.4 mg/kg/day in more severe infections (otitis media, sinusitis and lower respiratory tract infections)

There is no clinical information on patients under 2 months of age. Therefore dose recommendations cannot be given to this patient group.

Dosage recommendations according to body weight
80 mg/mL oral suspension (1 mL oral suspension = 80 mg amoxicillin)

Weight (kg)	25/3.6 mg/kg/day (mL twice daily)*	45/6.4 mg/kg/day (mL twice daily)*
3	0.5	0.8
4	0.6	1.1
5	0.8	1.4
6	0.9	1.7
7	1.1	2.0
8	1.3	2.3
9	1.4	2.5
10	1.6	2.8
11	1.7	3.1
12	1.9	3.4
13	2.0	3.7
14	2.2	3.9
15	2.3	4.2
16	2.5	4.5
17-21	2.5	5.0
22-29	4.0	7.5
30-40	5.0	10.0

*The 35 mL presentation is supplied with a syringe dosing device

Usual recommended daily dosage for adults
1,760 mg per day (11.0 mL twice daily)

Dosage in renal functional impairment
The dose should be reduced in patients with renal functional impairment depending on the severity of the impairment and the patient's weight.
Amoxicillin/clavulanic acid powder for oral suspension should only be used in patients with a GFR > 30 mL/min.

Dosage in hepatic functional impairment
Administer with caution. The liver function should be monitored at regular intervals. The experience in the use of the product in hepatic insufficiency is not adequate in order to give dose recommendations.

Method of administration
Amoxicillin/clavulanic acid is recommended to be taken at the start of meals to reduce any possible gastrointestinal discomfort.

Duration of administration
As a rule, amoxicillin/clavulanic acid powder for oral suspension is administered for a further 3 to 4 days after improvement/ regression of the symptoms and should be continued, however, for at least the generally recommended minimum period of treatment. Treatment should not be extended beyond 14 days without review.

As a precaution, therapy over at least 10 days is indicated in the treatment of infections with β-hemolytic streptococci in order to guard against late complications (e.g. rheumatic fever, glomerulonephritis).

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. cephalosporins, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see Undesirable effects)

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 Contraindications and Undesirable effects).

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 organism(s) the consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

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

Convulsions may occur in patients with impaired renal function or in those receiving high dose (see Undesirable effects).

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 likelikood 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 Undesirable effects). This reaction requires Amoxicillin/clavulanic acid discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see Dosage and administration, Contraindications and Undesirable effects).

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 Undesirable effects).

Antibiotic-associated colitis have been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see Undesirable effects). Therefore, it is important to consider this diagnosis in patients who present with diarrhea 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 hematopoietic 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 desirable level of anticoagulation (see Interaction with other medicinal products and other forms of interaction and Undesirable effects).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see Dosage and administration).
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 Overdose).

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 amoxicillin/clavulanic acid 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 polyfuranose 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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 Special warnings and precautions for use and Undesirable effects).

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.

PREGNANCY AND LACTATION

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

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

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 Undesirable effects).

UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions (ADRs) are diarrhea, 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)

Infections and infestations	
Common	Mucocutaneous candidosis
Not known	Overgrowth of non-susceptible organism
Blood and lymphatic system disorders	
Rare	Reversible leucopenia (including neutropenia), thrombocytopenia
Not known	Reversible agranulocytosis, haemolytic anemia, prolongation of bleeding time and prothrombin time[1]
Immune systems disorders[10]	
Not known	Angioneurotic oedema, anaphylaxis, serum sickness like syndrome, hypersensitivity vasculitis
Nervous system disorders	
Uncommon	Dizziness, headache
Not known	Reversible hyperactivity, convulsions[2], aseptic meningitis
Gastrointestinal disorders	
Common	Diarrhoea, nausea[3], vomiting
Uncommon	Indigestion
Not known	Antibiotic-associated colitis[4], back hairy tongue, tooth discoloration[11]
Hepatobiliary disorders	
Uncommon	Rises in AST and/or ALT[5]
Not known	Hepatitis[6], Cholestatic jaundice[6]
Skin and subcutaneous tissue disorder[7]	
Uncommon	Skin rash, Pruritus, Urticaria
Rare	Erythema multiforme
Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalized exanthemous pustulosis (AGEP)[9] and drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders	
Not known	Interstitial nephritis, crystalluria[8]

[1] See Special warnings and precautions for use
[2] See Special warnings and precautions for use
[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 (see Special warnings and precautions for use)
[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 Special warning and precautions for use).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see Special warnings and precautions for use).
[8] See Oversdose
[9] See Special warnings and precautions for use
[10] See Contraindications and Special warning and precautions for use
[11] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; beta-lactam antibacterials, penicillins; combinations or penicillins, including 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 synthesis leads to weakening of the 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 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 mechanism 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 mechanism 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 (µg/mL)	
	Susceptible ≤	Intermediate >
Enterobacteriaceae	8 [1,2]	8 [2]
	32 [1,2,3]	32 [1,2,3]
Staphylococcus spp	Note [4,5]	Note [4,5]
Enterococcus [6]	4 [2]	8 [2]
Streptococcus A, B, C, G [7]	Note [8]	Note [8]
Streptococcus pneumoniae [3]	Note [9,10,11]	Note [9,10,11]
Viridans group *streptococci*	Note [12]	Note [12]
Haemophilus influenzae [13]	2 [2]	2 [2]
Moraxella catarrhalis [14]	1 [2]	1 [2]
Neisseria gonorrhoeae	Note [15]	Note [15]
Gram-positive anaerobes except *Clostridium difficile*	4 [2]	8 [2]
Gram-negative anaerobes	4 [2]	8 [2]
Pasteurella multocida	1 [2]	1 [2]
Kingella kingae	Note [16]	Note [16]
PK/PD (non-species related) breakpoints	2 [2]	8 [2]

[1] Wild type Enterobacteriaceae are categorized as susceptible to aminopenicillins. Some countries prefer to categorize wild type isolates of *E.coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoints S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm.
[2] For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
[3] Amoxicillin-clavulanic acid (uncomplicated UTI only)
[4] Most staphylocci are penicillinase producers, which are resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, piperacillin and ticarcillin. Isolates negative for penicillinase and susceptible to methicillin can be reported to these agents. Isolates positive for penicillinase and methicillin susceptible are susceptible to beta-lactamase inhibitor combinations and isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin). Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[5] Ampicillin susceptible *S. saprophyticus* are mecA-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).
[6] Susceptibility to ampicillin, amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferred from ampicillin.
[7] Streptococcus groups A, B, C, and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.
[8] The susceptibility of streptococcus groups A, B, C, and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolyl penicillins for streptococcus group B.
[9] Breakpoints for penicillins other than benzylpenicillin relate only to non-meningitis isolates. Isolates fully susceptible to benzylpenicillin (MIC ≤ 0.06 mg/mL and/or susceptible by oxacillin disk screen, see note) can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note").
[10] For isolates categorized as intermediate to ampicillin avoid oral treatment with ampicillin, amoxicillin or amoxicillin-clavulanic acid
[11] Susceptibility inferred from the MIC of ampicillin.
[12] For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.
[13] Breakpoints are based on intravenous administration.
[14] Most *M. catarrhalis* produce beta-lactamase, although beta-lactamase production is slow and may give weak results with *in vitro* tests. Beta-lactamases producers should be reported resistant to penicillins and aminopenicillins without inhibitors.
[15] Always test for beta-lactamase. If positive, report resistant to benzylpenicillin, ampicillin and amoxicillin. Tests based on chromogenic cephalosporin can be used to detect the beta-lactamase. The susceptibility of beta-lactamase negative isolates to ampicillin and amoxicillin can be inferred from benzylpenicllin.
[16] The intrinsic activity of clavulanic acid in *K. kingae* is such that the organism is inhibited by ≤ 2 mg/L clavulanic acid. Therefore no MIC breakpoints for amoxicillin-clavulanic acid can be given.

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)[£]
Streptococcus agalactiae
Streptococcus pneumoniae[1]
Streptococcus pyogenes and other beta-haemolytic streptococci
Streptococcus viridans group
Aerobic Gram-negative microorganisms
Capnocytophaga spp.
Eikenella corrodens
Haemophilus influenzae[2]
Moraxella catarrhalis
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 microorganism
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

[1] *Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see Special warnings and precautions for use.)
[2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

Pharmacokinetic properties

Absorption

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

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets two 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 (mg)	C_{max} (µg/mL)	T_{max}* (h)	AUC $_{(0-24H)}$ (µg•h/mL)	$T_{1/2}$ (h)
Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1, 5 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
AMX - amoxicillin, CA - clavulanic acid * Median (range)					

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

Distribution

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

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissue, synovial and peritoneal fluid, 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 Pregnancy and lactation).

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

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 of 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 hours after administration of single amoxicillin/clavulanic acid 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 Interaction with other medicinal products and other form of interaction).

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 new borns) 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 functions, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

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

Renal impairment

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

Hepatic impairment

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

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.

PHARMACEUTICAL PARTICULARS

Incompatibilities
Not applicable

DIRECTION FOR RECONSTITUTION

Fill the bottle with drinking water to just below the filling mark and shake well at once. Then add water to the filling mark and shake vigorously again. Shake the bottle well before every withdrawal.

SPECIAL PRECAUTIONS FOR STORAGE

Powder for suspension: Store at temperatures not exceeding 30°C.
The reconstituted suspension should be stored in a refrigerator (2° - 8°C) and used within 7 days.
Keep in the original container. Keep the container tightly closed.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek advice from a healthcare professional at the first sign of any adverse drug reaction.

AVAILABILITY

70 mL Amber Glass Bottle with Plastic Syringe

Drug Registration Number: DRP-2274-03

Date of First Authorization: 04 April 2019

DATE OF REVISION

August 2019 (CDS v04)

Marketing Authorization Holder
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