NAME OF MEDICINAL PRODUCT

Augmentin 500mg/62.5mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Strength[1] (amoxicillin/clavulanate)	**Strength (co-amoxiclav)**	**Ratio (amoxicillin:clavulanate)**
Powder for oral suspension (in sachets)		
500/62.5 mg	562.5 mg	8:1
[1] Amoxicillin is present as amoxicillin trihydrate. Clavulanate is present as potassium clavulanate.		

Excipients

Silicon Dioxide, Crospovidone, Lemon-Peach-Strawberry Dry Flavour, Aspartame.

CLINICAL INFORMATION

General description

Amoxicillin-clavulanate (beta-lactam antibacterial penicillin coformulated with a beta-lactamase inhibitor) is an antibiotic agent with a notably broad-spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxycillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics.

Indications

Amoxicillin-clavulanate should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Adult formulations

Amoxicillin-clavulanate is indicated for short term treatment of bacterial infections at the following sites when caused by amoxicillin-clavulanate-susceptible organisms:

- Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media, typically caused by *Streptococcus pneumoniae, Haemophilus influenzae*[#]*, Moraxella catarrhalis*[#] and *Streptococcus pyogenes.*

- Lower respiratory tract infections e.g. acute exacerbation of chronic obstructive pulmonary disease (AECOPD)/acute exacerbations of chronic bronchitis (AECB), lobar and bronchopneumonia, typically caused by *Streptococcus pneumoniae, Haemophilus influenzae*[#] and *Moraxella catarrhalis*[#].

- Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, female genital infections typically caused by *Enterobacteriaceae** (mainly *Escherichia coli*[#]), *Staphylococcus saprophyticus* and *Enterococcus species* and gonorrhoea caused by *Neisseria gonorrhoeae*[#].

- Skin and soft tissue infections typically caused by *Staphylococcus aureus*[#], *Streptococcus pyogenes* and *Bacteroides species*[#].

- Bone and joint infections e.g. osteomyelitis typically caused by *Staphylococcus aureus*[#], where more prolonged therapy may be appropriate.

- Other Infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

Paediatric formulations

Amoxicillin-clavulanate is indicated for short term treatment of bacterial infections at the following sites when caused by amoxicillin-clavulanate sensitive organisms:

- Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media typically caused by *Streptococcus pneumoniae, Haemophilus influenzae*[#], *Moraxella catarrhalis*[#] and *Streptococcus pyogenes.*

- Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia typically caused by *Streptococcus pneumoniae, Haemophilus influenzae*[#] and *Moraxella catarrhalis*[#].

- Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, female genital infections typically caused by *Enterobacteriaceae*[#] (mainly *Escherichia coli*[#]) *Staphylococcus saprophyticus* and *Enterococcus* species, and gonorrhoea caused by *Neisseria gonorrhoeae*[#].

- Skin and soft tissue infections typically caused by *Staphylococcus aureus*[#], *Streptococcus pyogenes* and *Bacteroides* species[#].

Amoxicillin-clavulanate Paediatric three times daily.

The paediatric three times daily dosing regimen is also indicated for the following infections:

- Bone and joint infections e.g. osteomyelitis typically caused by *Staphylococcus aureus*[#], where more prolonged therapy may be appropriate.

- Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

[#] Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone (see *Clinical Pharmacology, Pharmacodynamic effects* for further information).

Susceptibility to amoxicillin-clavulanate 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 amoxicillin-clavulanate treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with amoxicillin-clavulanate-susceptible beta-lactamase-producing organisms may therefore be treated by amoxicillin-clavulanate.

Dosage and Administration

Dosage depends on the age, weight and renal function of the patient and the severity of the infection.

Dosages are expressed throughout in terms of amoxicillin-/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal.

The absorption of amoxicillin-clavulanate is optimised when taken at the start of a meal.

Treatment should not be extended beyond 14 days without review.

Therapy can be started parenterally and continued with an oral preparation

Populations

Adults

Formulation Ratio (amoxicillin: clavulanate)	**Mild to moderate infections**	**Severe infections** Including chronic and recurrent urinary tract infections and infections of the lower respiratory tract.
8:1	1000/125 mg given twice daily	1000/125 mg given 3 times daily

Children

Dosage should be expressed in terms of the age of the child and either in mg/kg/day (given in 2 or 3 divided doses).

Children weighing 40 kg and over should be dosed according to the adult recommendations.

Children up to 12 years

Formulation ratio (amoxicillin: clavulanate)	**Lower dose** Recommended for infections such as skin and soft tissue and recurrent tonsillitis.	**Higher dose** Recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections.
8:1	40/5 mg/kg/day given as 3 divided doses [(1)]	80/10 mg/kg/day given as 3 divided doses [(1)]

[(1)] There are no clinical data for the 8:1 formulation for patients under 1 month of age. Dosing recommendations in this population therefore cannot be made.

Premature

No dosage recommendation can be made for this category.

- *Elderly*

No adjustment needed, dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

- *Renal impairment*

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

Adults

Creatinine clearance greater than 30 ml/min	No adjustment necessary.

The 8:1 presentation should only be used in patients with a creatinine clearance of more than 30 mL/min.

Children

Creatinine clearance greater than 30 ml/min	No adjustment necessary.

The 8:1 presentation should only be used in patients with a creatinine clearance of more than 30 mL/min.

In the majority of cases, parenteral therapy, where available, may be preferred.

Haemodialysis

Adults

1 times 500/125 mg OR 2 times 250/125 mg every 24 hours, **PLUS** 1 dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin *and clavulanic acid are decreased).* (+)

(+) The 8:1 presentation should only be used in patients with a creatinine clearance of more than 30 mL/min.

Children

15/3.75 mg/kg/day given as a single daily dose.

Prior to haemodialysis one additional dose of 15/3.75 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15/3.75 mg/kg should be administered after haemodialysis. (+)

(+) The 8:1 presentation should only be used in patients with a creatinine clearance of more than 30 ml/min.

Hepatic impairment

Administer with caution; monitor hepatic function at regular intervals.

There are insufficient data on which to base a dosage recommendation.

Contraindications

Amoxicillin-clavulanate 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.

Warnings and Precautions

Before initiating therapy with amoxicillin-clavulanate, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

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 (see *Contraindication*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin-clavulanate (see *Adverse Reactions*). Drug-induced enterocolitis syndrome has been reported mainly in children receiving amoxicillin-clavulanate (*see Adverse Reactions*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and appropriate alternative therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management, including intubation may also be required.

Amoxicillin-clavulanate 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.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

In general amoxicillin-clavulanate is well tolerated and possesses the characteristic low toxicity of the penicillin group of antibiotics. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Amoxicillin-clavulanate should be used with caution in patients with evidence of hepatic dysfunction.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see *Dosage and Administration − Renal impairment*).

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 (see *Overdosage*).

Amoxicillin-clavulanate Sachets, contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

Interactions

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin-clavulanate may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of amoxicillin-clavulanate and allopurinol.

In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature, there are rare 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.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Pregnancy and Lactation

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Lactation

Amoxicillin-clavulanate may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

Ability to perform tasks that require judgement, motor or cognitive skills

Adverse effects on the ability to drive or operate machinery have not been observed.

Adverse Reactions

Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

very common ≥1/10

common ≥1/100 to <1/10

uncommon ≥1/1000 to <1/100

rare ≥1/10,000 to <1/1000

very rare <1/10,000.

Infections and infestations

Common	Mucocutaneous candidiasis.

Blood and lymphatic system disorders

Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia.
Very rare	Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare	Angioneurotic oedema, anaphylaxis *(see Warnings and Precautions)*, serum sickness-like syndrome, hypersensitivity vasculitis (*see also Skin and subcutaneous tissue disorders*).

Nervous system disorders

Uncommon	Dizziness, headache.
Very rare	Reversible hyperactivity, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very rare	Kounis syndrome (see Warnings and Precautions).

Gastrointestinal disorders

Adults:

Very common	Diarrhoea.
Common	Nausea, vomiting.

Children:

Common	Diarrhoea, nausea, vomiting.

All populations:

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin-clavulanate at the start of a meal.

Uncommon	Indigestion.
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), drug-induced enterocolitis syndrome. (see *Warnings and Precautions*).Black hairy tongue. 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.

Hepatobiliary disorders

Uncommon	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.
Very rare	Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

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.

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.

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria.
Rare	Erythema multiforme.
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (*see also Immune system disorders*). If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease.

Renal and urinary disorders

Very rare	Interstitial nephritis, crystalluria (see *Overdosage*).

Overdosage

Symptoms and Signs

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 *Warnings and Precautions*).

Treatment

GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin-clavulanate can be removed from the circulation by haemodialysis.

Children

A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Drug abuse and dependence

Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Anatomical Therapeutic Chemical (ATC) code: J01CR02
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

Mechanism of Action

Amoxicillin is a semisynthetic antibiotic with a broad-spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by beta-lactamases 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 the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.

The presence of clavulanic acid in amoxicillin-clavulanate formulations protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus amoxicillin-clavulanate

possesses the distinctive properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacodynamic Effects

In the list below, organisms are categorised according to their *in vitro* susceptibility to amoxicillin-clavulanate.

***In vitro* susceptibility of micro-organisms to amoxicillin-clavulanate** Where clinical efficacy of amoxicillin-clavulanate has been demonstrated in clinical trials this is indicated with an asterisk (*). Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxicillin, it can be considered susceptible to amoxicillin-clavulanate.
Commonly susceptible species
Gram-positive aerobes: *Bacillius anthracis* *Enterococcus faecalis* *Listeria monocytogenes* *Nocardia asteroides* *Streptococcus pyogenes**† *Streptococcus agalactiae**† *Streptococcus* spp. (other beta-hemolytic) *† *Staphylococcus aureus* (methicillin susceptible)* *Staphylococcus saprophyticus* (methicillin susceptible) Coagulase negative staphylococcus (methicillin susceptible)
Gram-negative aerobes: *Bordetella pertussis* *Haemophilus influenzae** *Haemophilus parainfluenzae* *Helicobacter pylori* *Moraxella catarrhalis** *Neisseria gonorrhoeae*

Pasteurella multocida *Vibrio cholerae*
Other: *Borrelia burgdorferi* *Leptospira ictterohaemorrhagiae* *Treponema pallidum*
Gram positive anaerobes: *Clostridium* spp. *Peptococcus niger* *Peptostreptococcus magnus* *Peptostreptococcus micros* *Peptostreptococcus* spp.
Gram-negative anaerobes: *Bacteroides fragilis* *Bacteroides* spp. *Capnocytophaga* spp. *Eikenella corrodens* *Fusobacterium nucleatum* *Fusobacterium* spp. *Porphyromonas* spp. *Prevotella* spp.
Species for which acquired resistance may be a problem

Gram-negative aerobes: *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Klebsiella* spp. *Proteus mirabilis* *Proteus vulgaris* *Proteus* spp. *Salmonella* spp. *Shigella* spp.
Gram-positive aerobes: *Corynebacterium* spp. *Enterococcus faecium* *Streptococcus pneumoniae**[†] Viridans group streptococcus
Inherently resistant organisms
Gram-negative aerobes: *Acinetobacter* spp. *Citrobacter freundii* *Enterobacter* spp. *Hafnia alvei* *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* spp. *Serratia* spp. *Stenotrophomas maltophilia* *Yersinia enterolitica*
Others:

Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia spp.
Coxiella burnetti
Mycoplasma spp.

Pharmacokinetics

Absorption

The two components of amoxicillin-clavulanate, 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-clavulanate is optimised when taken at the start of a meal.

Amoxicillin serum concentrations achieved with amoxicillin-clavulanate are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution

Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein.

From animal studies, there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

Metabolism

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose.Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

Elimination

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms.

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 250/125 mg or a single 500/125 mg tablet.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (*see Interactions*).

NON-CLINICAL INFORMATION

No further information of relevance.

PHARMACEUTICAL INFORMATION

Shelf-Life and Storage Condition

Store in a dry place in the original package to protect from moisture.
Please refer to the packaging.

Nature and Contents of Container

Amoxicillin-clavulanate powder for reconstitution is supplied in single-use sachets.
Box/ 12 Sachets.

Incompatibilities

None known.

Use and Handling

Check the sachet is intact before use. Sachet contents should be stirred into water before taking.

For administration to children up to 2 years old, amoxicillin-clavulanate suspensions may be diluted to half-strength using water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by:

Glaxo Wellcome Production

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