AUGMENTIN™ TID TABLETS AND SUSPENSION

Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Augmentin™ 156 mg/5 ml suspension: When reconstituted each 5 ml contains 125 mg amoxicillin (as amoxicillin trihydrate) and 31.25 mg clavulanic acid (as potassium clavulanate).
Augmentin™ 312 mg/5 ml suspension: When reconstituted each 5 ml contains 250 mg amoxicillin (as amoxicillin trihydrate) and 62.5 mg clavulanic acid (as potassium clavulanate).
Augmentin™ 625 mg tablets: Each film-coated tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate).
For a full list of excipients, see section 'List of Excipients'.

PHARMACEUTICAL FORMS

Augmentin™ 156 mg/5 ml suspension: Powder for oral suspension. Dry powder for reconstitution in water, at time of dispensing, to form fruit flavoured suspension.
Augmentin™ 312 mg/5 ml suspension: Powder for oral suspension. Dry powder for reconstitution in water, at time of dispensing, to form fruit flavoured suspension.
Augmentin™ 625 mg tablets: Film-coated tablet. White to off-white, oval film-coated tablets debossed with 'AC' and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

CLINICAL PARTICULARS

Therapeutic Indications

Augmentin™ is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- 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

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

Posology and Method of Administration

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 Augmentin™ that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents.
- 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 Augmentin™ (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.
For adults and children ≥ 40 kg, these formulations of Augmentin™ provide a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, these formulations of Augmentin™ provide a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin™ is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.
The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see *Warnings and Precautions for Use* regarding prolonged therapy).

Adults and children ≥ 40 kg

One 500 mg/125 mg dose taken three times a day.

Children < 40 kg

20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.
Children may be treated with Augmentin™ tablets, suspensions or paediatric sachets. Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.

For Augmentin™ 625 mg tablets:

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Augmentin tablets.
The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

No clinical data are available on doses of Augmentin™ 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

Elderly

No dose adjustment is considered necessary.

Renal impairment

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

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml/min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections *Contraindications* and *Warnings and Precautions*).

Method of administration

Augmentin™ is for oral use.
Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.
Therapy can be started parenterally according the prescribing information of the IV-formulation and continued with an oral preparation.
For Augmentin™ 156 mg/5 ml suspension and Augmentin™ 312 mg/5 ml suspension:
Shake to loosen powder, add water as directed, invert and shake.
Shake the bottle before each dose (See *Instructions for Use/Handling*).

Contraindications

Amoxicillin-clavulanate is contra-indicated

- 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 (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, 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.
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.
Amoxicillin-clavulanate Suspensions/Sachets/Chewable Tablets (where applicable), 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.

Pregnancy and Lactation

Fertility

No Text.

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 and <1/10
uncommon >1/1000 and <1/100
rare >1/10,000 and <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, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders

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

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).
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*.

*This statement is core safety for the syrup, suspension and chewable tablet formulations.

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.

Children (additional statement):

These events have been very rarely reported in children.

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.

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)

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Renal and urinary disorders

Very rare — Interstitial nephritis, crystalluria.

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.

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 (additional statement):

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.

PHARMACEUTICAL DATA

List of Excipients

Augmentin™ 156 mg/5 ml suspension and Augmentin™ 312 mg/5 ml suspension:
The powder contains xanthan gum, hydroxypropyl methylcellulose, aspartame, silicon dioxide, colloidal silica, succinic acid, raspberry, orange and golden syrup dry flavours.
Augmentin™ 625 mg tablets:
Each tablet contains magnesium stearate, sodium starch glycollate, colloidal silica, microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol and silicone oil.

Incompatibilities

None.

Shelf life

Augmentin™ 156 mg/5 ml suspension and Augmentin™ 312 mg/ 5ml suspension:
Dry powder: As indicated on outer packaging.
Reconstituted suspensions: should be kept in a refrigerator (but not frozen) and used within 7 days.
Augmentin™ 625 mg tablets:
As indicated on outer packaging.
Tablets in desiccated pouch packs should be used within 30 days of opening.

Special precautions for storage

Store in a dry place at 30°C or below.
Augmentin™ 156 mg/5 ml suspension and Augmentin™ 312 mg/ 5ml suspension:
Before reconstitution, keep tightly closed and store in a dry place at 30°C or below.
Once reconstituted, store in a refrigerator and use within 7 days.
Do not freeze.
Augmentin™ 625 mg tablets:
Store in the original package in order to protect from moisture.
Use within 30 days of opening.

Nature and Contents of Container

Augmentin™ 156 mg/5 ml suspension: Clear glass bottles containing powder for reconstitution to 100 ml. The bottle is supplied in a carton.
Augmentin™ 312 mg/5 ml suspension: Clear glass bottles containing powder for reconstitution to 60 or 100 ml or 20 ml (with a plastic dosing syringe). The 100 ml bottle is supplied in a carton.
Augmentin™ 625 mg tablets: A carton containing 20 tablets in blisters inside a desiccated pouch.
Not all pack sizes may be marketed.

Instructions for Use/Handling

Augmentin™ 625 mg tablets: None
Augmentin™ 156 mg/5 ml suspension and Augmentin™ 312 mg/ 5ml suspension:
When first reconstituted allow to stand for 5 minutes to ensure full dispersion.
Check cap seal is intact before using. Shake bottle to loosen powder. Add volume of water (as indicated below) invert and shake well. Alternatively fill the bottle with water to just below the mark on bottle label, invert and shake well, then top up with water exactly to the mark, invert and again shake well.

Strength	Volume of water to be added at reconstitution (ml)	Final volume of reconstituted oral suspension (ml)
156 mg /5 ml	92	100
312 mg /5 ml	90	100

Shake the bottle well before each dose.

Manufactured by:
SmithKline Beecham Limited*
Worthing, United Kingdom
*Member of the GlaxoSmithKline group of companies

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.