AUGMENTIN TID TABLETS AND SUSPENSION

Amoxycillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 375 mg tablets: Each tablet contains 250 mg amoxycillin (as amoxycillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

AUGMENTIN 625 mg tablets: Each tablet contains 500 mg amoxycillin (as amoxycillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

AUGMENTIN 1 g tablets: Each tablet contains 875 mg Amoxycillin (as the Amoxycillin trihydrate B.P) and 125 mg clavulanic acid (as the potassium salt B.P).

AUGMENTIN suspension 156.25 mg/5 mL: When reconstituted each 5 mL contains 125 mg amoxycillin (as amoxycillin trihydrate) and 31.25 mg clavulanic acid (as potassium clavulanate).

AUGMENTIN suspension 312.5 mg/5 mL: When reconstituted each 5 mL contains 250 mg amoxycillin (as amoxycillin trihydrate) and 62.5 mg clavulanic acid (as potassium clavulanate).

PHARMACEUTICAL FORM

AUGMENTIN 375 mg tablets: A white to off-white oval-shaped film-coated tablet, debossed with ‘Augmentin’ on one side.

AUGMENTIN 625 mg tablets: A white to off-white oval-shaped film-coated tablet, debossed with ‘AC’ and a score line on one side and plain on the other side.

AUGMENTIN 1 g tablets: A white oval-shaped film-coated tablet engrained debossed with ‘AC’ and a break line on the other.

AUGMENTIN suspension 156.25 mg/5 mL: An off-white dry powder for reconstitution in water to form a fruit flavoured suspension.

AUGMENTIN suspension 312.5 mg/5 mL: An off-white dry powder for reconstitution in water to form a fruit flavoured suspension.

CLINICAL PARTICULARS

Indications

AUGMENTIN 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.

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

AUGMENTIN oral presentations for three times daily dosing, are indicated for short-term treatment of bacterial infections at the following sites:

Upper respiratory tract infections (including ENT) e.g. tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbation of chronic bronchitis, lobar and bronchopneumonia.

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections, e.g. boils, abscesses, cellulitis, wound infections.

Bone and joint infections e.g. osteomyelitis.

Dental infections e.g. dentoalveolar abscess.

Other infections e.g. intra-abdominal sepsis.

Susceptibility to *AUGMENTIN* will vary with geography and time (see *Pharmacological Properties, Pharmacodynamics* for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Infections caused by amoxycillin-susceptible organisms are amenable to *AUGMENTIN* treatment due to its amoxycillin content. Mixed infections caused by amoxycillin-susceptible organisms in conjunction with *AUGMENTIN*-susceptible beta-lactamase producing organisms may therefore be treated with *AUGMENTIN*.

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 amoxycillin/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 *AUGMENTIN* 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.

AUGMENTIN suspensions may be supplied with a plastic dosing device. For preparation of the suspensions see *Instructions for Use/Handling*.

Adults and Children over 12 years

AUGMENTIN tablets are not recommended in children of 12 years and under.

The usual recommended daily dosage is:

Mild - Moderate infections	One *AUGMENTIN* 375 mg tablet every 8 hours ***OR*** One *AUGMENTIN* 625 mg given 2 or 3 times daily.
Severe infections	One *AUGMENTIN* 1g tablet twice daily. ***OR*** Two *AUGMENTIN* 375 mg tablets every 8 hours ***OR*** One *AUGMENTIN* 625 mg tablet every 8 hours.

Children

The usual recommended daily dosage is:

- *Lower dose*: 20/5 to 40/10 mg/kg/day in three divided doses for mild to moderate infections (upper respiratory tract infections e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).
- *Higher dose*: 40/10 to 60/15 mg/kg/day in three divided doses for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections).

No clinical data are available on doses above 40/10 mg/kg/day in children under 2 years.

The tables below give dosage guidance for children.

Children 2 years and over

***AUGMENTIN* suspension 156.25 mg/5 mL**		
Body weight (kg)	For lower dose range (mL every 8 hours)	For higher dose range (mL every 8 hours)
10 to 14	5	7.5
15 to 18	7.5	10

***AUGMENTIN* suspension 312.5 mg/5 mL**		
Body weight (kg)	For lower dose range (mL every 8 hours)	For higher dose range (mL every 8 hours)
13 to 18	2.5	5
19 to 28	5	7.5
29 to 37	7.5	10
38 to < 40.0	10	12.5

Children under 2 years

***AUGMENTIN* suspension 156.25 mg/5 mL**		
Body Weight (kg)	Lower Dose at 20/5 mg/kg/day (mL every 8 hours)	Higher Dose at 40/10 mg/kg/day (mL every 8 hours)
1	0.3	0.5
2	0.5	1.1
3	0.8	1.6
4	1.1	2.1
5	1.3	2.7
6	1.6	3.2
7	1.9	3.7
8	2.1	4.3
9	2.4	4.8
10	2.7	5.3
11	2.9	5.9
12	3.2	6.4
13	3.5	6.9
14	3.7	7.5
15	4.0	8.0

***AUGMENTIN* suspension 312.5 mg/5 mL**		
Body Weight (kg)	Lower Dose at 20/5 mg/kg/day (mL every 8 hours)	Higher Dose at 40/10 mg/kg/day (mL every 8 hours)
1	0.1	0.3
2	0.3	0.5
3	0.4	0.8

4	0.5	1.1
5	0.7	1.3
6	0.8	1.6
7	0.9	1.9
8	1.1	2.1
9	1.2	2.4
10	1.3	2.7
11	1.5	2.9
12	1.6	3.2
13	1.7	3.5
14	1.9	3.7
15	2.0	4.0

Renal Impairment

Adults

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

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

CrCl 10-30 mL/min	The usual recommended dose of *AUGMENTIN* 375 mg ***OR*** *AUGMENTIN* 625 mg tablets given every **12 hours**.
CrCl < 10 mL/min	The usual recommended dose of *AUGMENTIN* 375 mg ***OR*** *AUGMENTIN* 625 mg tablets given every **24 hours**.
Haemodialysis	The usual recommended dose of *AUGMENTIN* 375 mg ***OR*** *AUGMENTIN* 625 mg tablets given every **24 hours**, plus a further dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxycillin and clavulanic acid are decreased).

Children

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

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

CrCl 10-30 mL/min	15/3.75 mg/kg every **12 hours** (maximum 500/125 mg every 12 hours).
CrCl < 10 mL/min	15/3.75 mg/kg every **24 hours** (maximum 500/125 mg).

Haemodialysis	15/3.75 mg/kg every **24 hours**. Prior to haemodialysis 15/3.75 mg/kg should be administered. In order to restore circulating drug levels, 15/3.75 mg/kg should be administered after haemodialysis.

Hepatic Impairment

Dose with caution; monitor hepatic function at regular intervals.

Each *AUGMENTIN* 375 mg tablet contains 0.63 mmol (25 mg) of potassium.

Contraindications

AUGMENTIN is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

AUGMENTIN is contraindicated in patients with a previous history of *AUGMENTIN*-associated jaundice/hepatic dysfunction.

Warnings and Precautions

Before initiating therapy with *AUGMENTIN*, 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 *Contraindications*). If an allergic reaction occurs, *AUGMENTIN* therapy must 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.

AUGMENTIN 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 amoxycillin.

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.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving *AUGMENTIN* 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.

Changes in liver function tests have been observed in some patients receiving *AUGMENTIN*. The clinical significance of these changes is uncertain but *AUGMENTIN* should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment *AUGMENTIN* dosage should be adjusted as recommended in the *Dosage and Administration* section.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxycillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxycillin crystalluria *(*see *Overdose).*

AUGMENTIN suspensions contain 12.5 mg aspartame per 5 mL dose, which is a source of phenylalanine, and therefore should be used with caution in patients with phenylketonuria.

Interactions

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin. Concomitant use with *AUGMENTIN* may result in increased and prolonged blood levels of amoxycillin but not of clavulanate.

Concomitant use of allopurinol during treatment with amoxycillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of *AUGMENTIN* and allopurinol.

In common with other antibiotics, *AUGMENTIN* 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 amoxycillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of *AUGMENTIN*.

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 amoxycillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Pregnancy and Lactation

Reproduction studies in animals (mice and rats) with orally and parenterally administered *AUGMENTIN* 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 *AUGMENTIN* may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

AUGMENTIN may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Data from large clinical trials were 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, serum sickness-like syndrome, hypersensitivity vasculitis

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.

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 *AUGMENTIN* at the start of a meal.

Uncommon	Indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis – 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), and drug reaction with eosinophilia and systemic symptoms (DRESS)

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

Renal and urinary disorders

Very rare	Interstitial nephritis, crystalluria *(*see *Overdose)*

Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance.

Amoxycillin crystalluria, in some cases leading to renal failure, has been observed *(*see *Warnings and Precautions).*

AUGMENTIN can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in *AUGMENTIN* anticipates this defence mechanism by blocking the beta-lactamase enzymes, thus rendering the

organisms susceptible to amoxycillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxycillin as *AUGMENTIN* it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

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

In vitro* susceptibility of micro-organisms to *AUGMENTIN
Where clinical efficacy of *AUGMENTIN* 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 amoxycillin, it can be considered susceptible to *AUGMENTIN*.
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

The pharmacokinetics of the two components of *AUGMENTIN* are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of *AUGMENTIN* is optimised at the start of a meal.

Doubling the dosage of *AUGMENTIN* approximately doubles the serum levels achieved.

Both clavulanate and amoxycillin have low levels of serum binding; about 70% remains free in the serum.

Pre-clinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

AUGMENTIN tablets contain magnesium stearate, sodium starch glycollate, colloidal silica, microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol and dimeticone (silicone oil).

AUGMENTIN dry powder for suspension contains xanthan gum, hydroxypropyl-methylcellulose, colloidal silica, succinic acid, silicon dioxide, aspartame, dry flavours (raspberry, orange and golden syrup).

AUGMENTIN presentations do not contain sucrose, tartrazine or any other azo dyes and *AUGMENTIN* suspensions do not contain preservatives.

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

AUGMENTIN oral presentations should be stored in a dry place at 25°C or below.

Bottles of AUGMENTIN tablets should be kept tightly closed and the tablets dispensed in moisture-proof containers.

Once reconstituted, AUGMENTIN suspension must be stored in a refrigerator (but not frozen) and used within 7 days.

Not all presentation are available in every country

Nature and Contents of Container

Augmentin tablet 375mg 6’s, 625mg 6’s and 1gm 6’s available in the pack of Aluminium foil pack.

AUGMENTIN 156.25 mg and 312.5 mg suspensions: Amber glass bottles with aluminium pilfer proof screw caps containing powder for reconstitution to 60 ml or 90 ml.

Not all presentation are available in every country

Instructions for Use/Handling

AUGMENTIN 375 mg and 625 mg tablets: None
AUGMENTIN 156.25 mg and 312.5 mg suspensions: At time of dispensing, the dry powder should be reconstituted to form an oral suspension as detailed below:

- Check cap seal is intact before use.
- Invert and shake bottle to loosen powder.
- Add volume of water (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 to the mark. Invert and shake again.
- Shake well before taking each dose.

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Strength	Volume of water to be added to reconstitute	Final volume of reconstituted oral suspension
156.25	55.0 ml	60 ml
312.50	55.0 ml	60 ml

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