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AUGMENTIN TID TABLETS AND SUSPENSION

Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 375 mg tablets: Each tablet contains 250 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).
AUGMENTIN 625 mg tablets: Each tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).
AUGMENTIN 156 mg 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 suspension: When reconstituted each 5 ml contains 250 mg amoxicillin (as amoxicillin 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 debossed tablet.
AUGMENTIN 625 mg tablets: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side.
AUGMENTIN 156 mg suspension: Bottles of powder for the preparation of fruit flavoured suspension.
AUGMENTIN 312 mg suspension: Bottles of powder for the preparation of 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 β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-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 amoxicillin -susceptible organisms are amenable to *AUGMENTIN* treatment due to its amoxicillin content. Mixed infections caused by amoxicillin -susceptible organisms in conjunction with *AUGMENTIN* -susceptible β-lactamase producing organisms may therefore be treated with *AUGMENTIN*.

Dosage and Administration

Usual dosages for the treatment of infection

Adults and children over 12 years	
Mild - Moderate infections	One *AUGMENTIN* 375 mg tablet 3 times a day.
Severe infections	One *AUGMENTIN* 625 mg tablet 3 times a day. Where the 625 mg tablet is not available, a dose of two *AUGMENTIN* 375 mg tablets 3 times a day may be taken. Therapy can be started parenterally and continued with an oral preparation.

Children:	
The usual recommended daily dosage is 25mg/kg/day* in divided doses every eight hours. The table below presents guidance for children.	
Under 1 year	25 mg/kg/day*, for example a 7.5 kg child would require 2 ml *AUGMENTIN* 156 mg suspension 3 times a day.
1-6 years (10-18 kg)	5 ml *AUGMENTIN* 156 mg suspension 3 times a day.
Over 6 years (18-40 kg)	5 ml *AUGMENTIN* 312 mg suspension 3 times a day.
In more serious infections the dosage may be increased up to 50 mg/kg/day in divided doses every eight hours.	

* Each 25 mg *AUGMENTIN* provides 20 mg amoxicillin and 5 mg clavulanate.
AUGMENTIN 375 mg and 625 mg tablets are not recommended in children of 12 years and under.

***Dosage in dental infections* (e.g. dentoalveolar abscess)**
Adults and children over 12 years: One *AUGMENTIN* 375 mg tablet 3 times a day for five days.

Dosage in renal impairment
Adults:

Mild impairment (Creatinine clearance >30 ml/min)	Moderate impairment (Creatinine clearance 10-30 ml/min)	Severe impairment (Creatinine clearance <10 ml/min)
No change in dosage.	One 375 mg tablet or one 625 mg tablet 12 hourly	Not more than one 375 mg tablet 12 hourly; 625 mg tablets are not recommended.

Children:

Mild impairment (Creatinine clearance >30 ml/min)	Moderate impairment (Creatinine clearance 10-30 ml/min)	Severe impairment (Creatinine clearance <10 ml/min)
No change in dosage.	18.75 mg/kg given twice daily (maximum 625 mg twice daily)	18.75 mg/kg given as a single daily dose (maximum 625 mg)

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.
Each *AUGMENTIN* 375 mg tablet contains 0.63 mmol (25 mg) of potassium.

Administration
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.

Contraindications
AUGMENTIN is contra-indicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.
AUGMENTIN is contra-indicated 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 (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 (see *Contraindications*).
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 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.
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 amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin 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 amoxicillin. Concomitant use with *AUGMENTIN* may result in increased and prolonged blood levels of amoxicillin but not of clavulanate.
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 *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 amoxicillin. 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 amoxicillin 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 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
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)
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.
Amoxicillin 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 β-lactamase enzymes, thus rendering the organisms susceptible to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.
Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin 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 amoxicillin, 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 β-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 amoxicillin 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 375 mg and 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.
AUGMENTIN 156 mg and 312 mg suspensions:
The powder contains xanthan gum, hydroxypropyl methylcellulose, aspartame, silicon dioxide, colloidal silica, succinic acid, raspberry, orange and golden syrup dry flavours.
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.

Nature and Contents of Container

AUGMENTIN 375 mg tablets: Blister packs of 20 in a carton.
AUGMENTIN 625 mg tablets: Blister packs of 20 in a carton.
AUGMENTIN 156 mg and 312 mg suspensions: Clear glass bottles with aluminium screw caps containing powder for reconstitution to 100 ml.

Instructions for Use/Handling

AUGMENTIN 375 mg and 625 mg tablets: None
AUGMENTIN 156 mg and 312 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.

Strength	Volume of water to be added to reconstitute	Final volume of reconstituted oral suspension
156	92 ml	100 ml
312	90 ml	100 ml

Not all presentations are available in every country.
Manufactured by:
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