Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION
AUGMENTIN 625mg tablets: Each tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).
AUGMENTIN 1g tablets: Each tablet contains 875 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

PHARMACEUTICAL FORM
AUGMENTIN 625mg 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 1g 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.

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 oral presentations for twice 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. septic abortion, puerperal sepsis, intra-abdominal sepsis.
A comprehensive list of susceptible organisms is provided in the Pharmacodynamics section.

Dosage and Administration
Usual dosages for the treatment of infection
Adults and children over 12 years+
Mild - Moderate infections - One AUGMENTIN 625mg tablet twice daily
Severe infections - One AUGMENTIN 1g tablet twice daily
Therapy can be started parenterally and continued with an oral preparation.

Dosage in dental infections (e.g. dentoalveolar abscess)
Adults and children over 12 years: One AUGMENTIN 625mg tablet two times a day for five days.
+ AUGMENTIN 625mg and 1g tablets are not recommended in children of 12 years and under

Dosage in renal impairment
Adults:
The AUGMENTIN 1g tablet should only be used in patients with a glomerular filtration rate of >30 ml/min.

<table>
<thead>
<tr>
<th>Mild impairment (Creatinine clearance &gt;30 ml/min)</th>
<th>Moderate impairment (Creatinine clearance 10-30 ml/min)</th>
<th>Severe impairment (Creatinine clearance &lt;10 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in dosage (i.e. either one 625mg tablet twice daily or one 1g tablet twice daily)</td>
<td>One 625mg tablet twice daily. The 1g tablet should not be administered.</td>
<td>Not more than one 625mg tablet every 24 hours.</td>
</tr>
</tbody>
</table>

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.
Administration
Tablets should be swallowed whole without chewing. If required, tablets may be broken in half and swallowed without chewing.
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.
AUGMENTIN is also available as AUGMENTIN intravenous for the short-term treatment of bacterial infections and for prophylaxis against infection which may be associated with major surgical procedures. AUGMENTIN intravenous is described in a separate Pack Insert.
AUGMENTIN is also available as a suspension for three times daily dosing for administration to children under the age of 12 years for the treatment of bacterial infections. AUGMENTIN suspension three times daily is described in a separate Pack Insert.

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 (anaphylactic) 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 Contra-indications).
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.
Prolongation of bleeding time and prothrombin time have been reported in some patients receiving AUGMENTIN. AUGMENTIN should be used with care in patients on anti-coagulation therapy.
Changes in liver function tests have been observed in some patients receiving AUGMENTIN. The clinical significance of these changes is uncertain. 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).

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.

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 preterm, 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 in 10
- common: ≥1 in 100 and <1 in 10
- uncommon: ≥1 in 1,000 and <1 in 100
- rare: ≥1 in 10,000 and <1 in 1,000
- 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 (see Warnings and Precautions).

**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 AUGMENTIN at the start of a meal.

Uncommon: Indigestion

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Black hairy tongue

**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.
AUGMENTIN is bactericidal to a wide range of organisms including:

**Gram-positive**
Aerobes: Enterococcus faecalis, Streptococcus pneumoniae
Gram-negative
Anaerobes: *Bacteroides spp. including B. fragilis.
* including β-lactamase producing strains resistant to ampicillin and amoxicillin.

**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 625 mg and 1 g tablets contain the following inactive ingredients: colloidal silicon dioxide, sodium starch glycolate, magnesium stearate (E572), microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol, dimethicone (silicon oil).

**Incompatibilities**
None known.
Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
AUGMENTIN tablets should be stored in unopened, original packs in a dry place at below 25°C. Not all presentations are available in every country.
Version number: GDS017/IPI06
Date of issue: 14 March 2007
AUGMENTIN is a trademark of:
the GlaxoSmithKline group of companies
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.

A comprehensive list of susceptible organisms is provided in the Pharmacodynamics section.
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 three times a day.
Severe infections: One AUGMENTIN 625 mg tablet three times a day.

Therapy can be started parenterally and continued with an oral preparation.

Children:
The usual recommended daily dosage is 25 mg/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 three times a day.
1-6 years (10-18 kg): 5 ml AUGMENTIN 156 mg suspension three times a day.
Over 6 years (18-40 kg): 5 ml AUGMENTIN 312 mg suspension three 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 three times a day for five days.

**Dosage in renal impairment**

**Adults:**

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

**Children:**

<table>
<thead>
<tr>
<th>Mild impairment (Creatinine clearance &gt;30 ml/min)</th>
<th>Moderate impairment (Creatinine clearance 10-30 ml/min)</th>
<th>Severe impairment (Creatinine clearance &lt;10 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in dosage.</td>
<td>18.75 mg/kg given twice daily (maximum 625 mg twice daily)</td>
<td>18.75 mg/kg given as a single daily dose (maximum 625 mg)</td>
</tr>
</tbody>
</table>

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 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 (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.

Prolongation of prothrombin time has been reported rarely in patients receiving AUGMENTIN. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

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.

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 preterm, 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 in 10
- common: ≥1 in 100 and <1 in 10
- uncommon: ≥1 in 1,000 and <1 in 100
- rare: ≥1 in 10,000 and <1 in 1,000
- 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 (see Warnings and Precautions)

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). 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.

AUGMENTIN is bactericidal to a wide range of organisms including:

**Gram-positive**


Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

**Gram-negative**

Anaerobes: *Bacteroides* spp. including *B. fragilis*. *including β-lactamase producing strains resistant to ampicillin and amoxicillin.

**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 25oC 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 mg suspensions: At time of dispensing, the dry powder should be reconstituted to form an oral suspension as detailed below:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of water to be added to reconstitute</th>
<th>Final volume of reconstituted oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>92 ml</td>
<td>100 ml</td>
</tr>
<tr>
<td>312</td>
<td>90 ml</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

Not all presentations are available in every country.

Version number: GDS18/PI08
Date of issue: 26 November 2007
AUGMENTIN is a trademark of: the GlaxoSmithKline group of companies.
Amoxicillin sodium - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION
AUGMENTIN 600 mg intravenous: 500 mg amoxicillin (as amoxicillin sodium) and 100 mg clavulanic acid (as potassium clavulanate) for reconstitution as an intravenous injection or infusion.
AUGMENTIN 1.2 g intravenous: 1 g amoxicillin (as amoxicillin sodium) and 200 mg clavulanic acid (as potassium clavulanate) for reconstitution as an intravenous injection or infusion.

PHARMACEUTICAL FORM
Sterile powder for injection.

CLINICAL PARTICULARS
Indications
AUGMENTIN is indicated for short-term treatment of bacterial infections at the following sites:
Upper respiratory tract infections (including ENT) e.g. recurrent 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.
Other infections e.g. intra-abdominal sepsis.
AUGMENTIN intravenous is also indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastrointestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract.
A comprehensive list of susceptible organisms is provided in the Pharmacodynamics section.
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
Dosage for the treatment of infections
Adults and children over 12 years:
Usually 1.2 g eight hourly. In more serious infections, increase frequency to six-hourly intervals.

Children 3 months-12 years:
Usually 30 mg/kg* AUGMENTIN eight hourly. In more serious infections, increase frequency to six-hourly intervals.

Children 0-3 months:
30 mg/kg* AUGMENTIN every 12 hours in premature infants and in full term infants during the perinatal period, increasing to eight hours thereafter.
* Each 30 mg AUGMENTIN contains 25 mg amoxicillin and 5 mg clavulanate.

Adult dosage for surgical prophylaxis
The usual dose is 1.2 g AUGMENTIN intravenous given at the induction of anaesthesia. Operations where there is a high risk of infection, e.g. colorectal surgery, may require three, and up to four, doses of 1.2 g AUGMENTIN intravenous in a 24-hour period. These doses are usually given at 0, 8, 16 (and 24) hours. This regimen can be continued for several days if the procedure has a significantly increased risk of infection.
Clear clinical signs of infection at operation will require a normal course of intravenous or oral AUGMENTIN therapy post-operatively.

Dosage in renal impairment
Adults
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.

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. Prolongation of bleeding time and prothrombin time have been reported in some patients receiving AUGMENTIN. AUGMENTIN should be used with care in patients on anti-coagulation therapy.

If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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).

The presence of clavulanic acid in AUGMENTIN may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

### Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.

Each 1.2 g vial of AUGMENTIN contains 1.0 mmol of potassium and 3.1 mmol of sodium (approx.).

### Administration
AUGMENTIN intravenous may be administered either by intravenous injection or by intermittent infusion. It is not suitable for intramuscular administration.

### 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, 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).

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.

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. Prolongation of bleeding time and prothrombin time have been reported in some patients receiving AUGMENTIN. AUGMENTIN should be used with care in patients on anti-coagulation therapy.

If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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).

The presence of clavulanic acid in AUGMENTIN may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

### 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.

<table>
<thead>
<tr>
<th>Mild impairment (creatinine clearance &gt;30 ml/min)</th>
<th>Moderate impairment (creatinine clearance 10-30 ml/min)</th>
<th>Severe impairment (creatinine clearance &lt;10 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in dosage</td>
<td>1.2 g IV stat., followed by 600 mg IV 12 hourly</td>
<td>1.2 g IV stat., followed by 600 mg IV 24 hourly</td>
</tr>
</tbody>
</table>

Children
Similar reductions in dosage should be made for children.

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.

Each 1.2 g vial of AUGMENTIN contains 1.0 mmol of potassium and 3.1 mmol of sodium (approx.).
In common with other antibiotics, AUGMENTIN may affect the gut flora, leading to lower oestrogen reab-sorption and reduced efficacy of combined oral con-traceptives.

The presence of clavulanic acid in AUGMENTIN may cause a non-specific binding of IgG and albu-min by red cell membranes leading to a false posi-tive Coombs test.

**Pregnancy and Lactation**

**Use in Pregnancy**

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 preterm, 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.

**Use in Lactation**

AUGMENTIN may be administered during the peri-od 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 deter-mine the frequency of very common to rare unde-sirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-mar-keting 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:** ě1 in 10
- **common:** ě1 in 100 and <1 in 10
- **uncommon:** ě1 in 1,000 and <1 in 100
- **rare:** ě1 in 10,000 and <1 in 1,000
- **very rare:** ě1/10,000.

**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 pro-thrombin time (see Warnings and Precautions)

**Immune system disorders**

- **Very rare:** Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

**Nervous system disorders**

- **Uncommon:** Dizziness, headache
- **Very rare:** Convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

**Vascular disorders**

- **Rare:** Thrombophlebitis at the site of injection

**Gastrointestinal disorders**

- **Common:** Diarrhoea
- **Uncommon:** Nausea, vomiting, indigestion
- **Very rare:** Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) are less likely to occur after parenteral administration.

**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 find-ings 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.

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
it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice. AUGMENTIN is bactericidal to a wide range of organisms including:

**Gram-positive**
- Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

**Gram-negative**
- Anaerobes: Bacteroides species* (including Bacteroides fragilis), Fusobacterium species*.

* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

### Pharmacokinetics
The pharmacokinetics of the two components of AUGMENTIN are closely matched.

Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dosage of AUGMENTIN approximately doubles the serum levels achieved.

### 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.

Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

### 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 sensitive 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,
blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions. If AUGMENTIN is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

**Shelf Life**
The expiry date is indicated on the packaging.

**Special Precautions for Storage**
AUGMENTIN vials should be stored in a dry place below 25oC.

**Nature and Contents of Container**
Glass vials (Ph.Eur. type I) fitted with butyl rubber bungs and aluminium overseals containing sterile white powder.

**Instructions for Use/Handling**
600 mg vial: To reconstitute dissolve in 10 ml Water for Injections BP. (Final volume 10.5 ml)
1.2 g vial: To reconstitute dissolve in 20 ml Water for Injections BP. (Final volume 20.9 ml)
A transient pink coloration may appear during reconstitution. Reconstituted solutions are normally a pale, straw colour.

**Intravenous injection:**
The stability of AUGMENTIN intravenous solution is concentration dependent, thus AUGMENTIN intravenous should be used immediately upon reconstitution and given by slow intravenous injection over a period of 3-4 minutes.

AUGMENTIN intravenous solutions should be used within 20 minutes of reconstitution. AUGMENTIN may be injected directly into a vein or via a drip tube.

**Intravenous infusion:**
Alternatively, AUGMENTIN intravenous may be infused in Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v). Add, without delay*, 600 mg reconstituted solution to 50 ml infusion fluid or 1.2 g reconstituted solution to 100 ml infusion fluid (e.g., using a minibag or in-line burette). Infuse over 30-40 minutes and complete within four hours of reconstitution. For other appropriate infusion fluids, see Stability and Compatibility section.

*Solutions should be made up to full infusion volume immediately after reconstitution. Any residual antibiotic solutions should be discarded. Therapy can be started parenterally and continued with an oral preparation. Treatment should not be extended beyond 14 days without review.

**Stability and Compatibility**
Intravenous infusions of AUGMENTIN may be given in a range of different intravenous fluids. Satisfactory antibiotic concentrations are retained at 5oC and at room temperature (25oC) in the recommended volume of the following infusion fluids. If reconstituted and maintained at room temperature, infusions should be completed within the times stated.

<table>
<thead>
<tr>
<th>Intravenous infusion fluids</th>
<th>Stability period at 25oC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for Injections B.P.</td>
<td>4 hours</td>
</tr>
<tr>
<td>Sodium Chloride Intravenous Infusion B.P. (0.9% w/v)</td>
<td>4 hours</td>
</tr>
<tr>
<td>Sodium Lactate Intravenous Infusion B.P. (one-sixth molar)</td>
<td>4 hours</td>
</tr>
<tr>
<td>Compound Sodium Chloride Intravenous Infusion B.P. (Ringer’s Solution)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Compound Sodium Lactate Intravenous Infusion B.P. (Ringer-Lactate Solution; Hartmann’s Solution)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Potassium Chloride and Sodium Chloride Intravenous Infusion B.P.</td>
<td>3 hours</td>
</tr>
</tbody>
</table>

Reconstituted solutions should not be frozen. AUGMENTIN is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solutions of AUGMENTIN should therefore not be added to such infusions but may be injected into the drip tubing over a period of 3-4 minutes.

For storage at 5oC, the reconstituted solution should be added to pre-refrigerated infusion bags which can be stored for up to 8 hours. Thereafter, the infusion should be administered immediately after reaching room temperature.

<table>
<thead>
<tr>
<th>Intravenous infusion fluids</th>
<th>Stability period at 5oC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for Injections</td>
<td>B.P. 8 hours</td>
</tr>
<tr>
<td>Sodium Chloride Intravenous Infusion B.P. (0.9% w/v)</td>
<td>8 hours</td>
</tr>
</tbody>
</table>
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