AUGMENTIN® 625 / 1000 DUO
Amoxycillin and Potassium Clavulanate Tablets IP

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 625 DUO:
Each film-coated tablet contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin 500 mg
Potassium Clavulanate IP (as Potassium Clavulanate Diluted IP) equivalent to Clavulanic Acid 125 mg
 Colour: Titanium Dioxide IP

AUGMENTIN 1000 DUO:
Each film-coated tablet contains:
Amoxycillin trihydrate IP equivalent to Amoxycillin 875 mg
Potassium Clavulanate IP (as Potassium Clavulanate Diluted IP) equivalent to Clavulanic Acid 125 mg
 Colour: Titanium Dioxide IP

The amoxycillin is present as amoxycillin trihydrate and the clavulanic acid is present as potassium clavulanate.

PHARMACEUTICAL FORM

AUGMENTIN 625 DUO: White oval film-coated tablets

AUGMENTIN 1000 DUO: White oval film-coated tablets

CLINICAL PARTICULARS

Therapeutic 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 amoxycillin 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 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

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

**Posology and Method of Administration**

- **Usual dosages for the treatment of infection**

<table>
<thead>
<tr>
<th>Adults and children over 12 years*</th>
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</thead>
<tbody>
<tr>
<td>Mild - Moderate infections</td>
<td>One AUGMENTIN 625 mg tablet twice daily</td>
</tr>
<tr>
<td>Severe infections</td>
<td>One AUGMENTIN 1 g tablet twice daily or One AUGMENTIN 625 mg tablet 3 times a day</td>
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</tbody>
</table>

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 625 mg tablet 2 times a day for five days

  *AUGMENTIN* 625 mg and 1 g 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. <em>either</em> one 625 mg tablet twice daily <em>or</em> one 1 g tablet twice daily)</td>
<td>One 625 mg tablet twice daily. The 1 g tablet should not be administered.</td>
<td>Not more than one 625 mg tablet every 24 hours.</td>
</tr>
</tbody>
</table>

• **Dosage in hepatic impairment**

Dose with caution; monitor hepatic function at regular intervals.

**Method of Administration**

Tablet to be consumed in whole, not to be broken.

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.

**Special Warnings and Special Precautions for Use**

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 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 International Normalized Ratio (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. *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 *Posology and Method of 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).

**Interaction with Other Medicaments and Other Forms of Interaction**

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 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.

Undesirable Effects

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

**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 Special Warnings and Special Precautions for use.)

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.

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

*AUGMENTIN* can be removed from the circulation by haemodialysis.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

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:**

*Bacillus anthracis*

*Enterococcus faecalis*

*Listeria monocytogenes*

*Nocardia asteroides*

*Streptococcus pyogenes* *†*

*Streptococcus pyogenes* *†*
Streptococcus agalactiae*†

Streptococcus spp. (other β-hemolytic) *†

Staphylococcus aureus (methicillin susceptible)*

Staphylococcus saprophyticus (methicillin susceptible)

Coagulase negative staphylococcus (methicillin susceptible)

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
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<tbody>
<tr>
<td>Bordetella pertussis</td>
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<tr>
<td>Haemophilus influenzae*</td>
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<tr>
<td>Haemophilus parainfluenzae</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
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<tr>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
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<table>
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<tr>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td>Leptospira icterohaemorrhagiae</td>
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<tr>
<td>Treponema pallidum</td>
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<table>
<thead>
<tr>
<th>Gram positive anaerobes:</th>
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</thead>
<tbody>
<tr>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Peptococcus niger</td>
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<tr>
<td>Peptostreptococcus magnus</td>
</tr>
<tr>
<td>Peptostreptococcus micros</td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
</tr>
</tbody>
</table>

<p>| Gram-negative anaerobes: |</p>
<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative aerobes:</strong></td>
</tr>
<tr>
<td>Escherichia coli*</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
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<tr>
<td>Klebsiella pneumoniae*</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
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<tr>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>Proteus spp.</td>
</tr>
<tr>
<td>Salmonella spp.</td>
</tr>
<tr>
<td>Shigella spp.</td>
</tr>
<tr>
<td><strong>Gram-positive aerobes:</strong></td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td>Streptococcus pneumoniae*</td>
</tr>
<tr>
<td>Viridans group streptococcus</td>
</tr>
<tr>
<td><strong>Inherently resistant organisms</strong></td>
</tr>
</tbody>
</table>
**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.*

**Pharmacokinetic Properties**

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.
Preclinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

*AUGMENTIN* 625 mg and 1 g tablets contain the following inactive ingredients: magnesium stearate, colloidal anhydrous silica, sodium starch glycollate, microcrystalline cellulose, Opaspray KI-7000, ethyl cellulose, propylene glycol, hydroxypropyl methyl cellulose, methylene chloride, methanol and activated dimethicone.

Incompatibilities

None known

Shelf Life

18 months
The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store in a dry place below 25°C.

Keep out of reach of children.

Nature and Specification of Container

Aluminium strips

Instructions for Use/Handling

No specific instructions
For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.

Registered Office:
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Mumbai 400 030, India.

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