Co-Amoxiclav
Augmentin® ES
600mg/ 42.9mg per 5mL Powder for Suspension

PRODUCT DESCRIPTION
Co-amoxiclav (Augmentin® ES) 600mg/42.9mg per 5mL Powder for Suspension: Bottles of Off-white powder with a characteristic strawberry odour, which, when reconstituted in water at time of dispensing, yields an off-white suspension. Each 5mL of reconstituted suspension contains 600mg amoxicillin and 42.9mg clavulanic acid.

The amoxicillin is present as amoxicillin trihydrate and the clavulanic acid is present as potassium clavulanate in a ratio of 14:1.

PHARMACOLOGIC PROPERTIES
Pharmacodynamics
Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

The clavulanic component in Co-amoxiclav (Augmentin® ES) protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, Co-amoxiclav (Augmentin® ES) possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

In the list below, organisms are categorised according to their in vitro susceptibility to Co-amoxiclav (Augmentin®).

In vitro susceptibility of micro-organisms to Co-amoxiclav (Augmentin®)

Where clinical efficacy of Co-amoxiclav (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 Co-amoxiclav (Augmentin®).

Commonly susceptible species

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus anthracis</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
</tr>
<tr>
<td>Nocardia asteroides</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Viridans group streptococcus†</td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp. (other β-hemolytic) d</td>
<td></td>
</tr>
<tr>
<td>Staphyloccocus aureus (methicillin susceptible)*</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus saprophyticus (methicillin susceptible)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordetella pertussis</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
<td></td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td></td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td></td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrelia burgdorferi</td>
<td></td>
</tr>
<tr>
<td>Leptospiira icterohaemorrhagiae</td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram positive anaerobes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium spp.</td>
<td></td>
</tr>
<tr>
<td>Peptococcus niger</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus magnus</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus micros</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
<td></td>
</tr>
</tbody>
</table>
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

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**
Pharmacokinetic parameters are given below for Co-amoxiclav (Augmentin® ES) administered at 45mg/kg every 12 hours to paediatric patients

<table>
<thead>
<tr>
<th>Formulation</th>
<th>C max (mg/L)</th>
<th>T max (hours)</th>
<th>AUC (mg.h/L)</th>
<th>T ½ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-amoxiclav (Augmentin® ES) 600/42.9 mg/5ml</td>
<td>15.7</td>
<td>2.0</td>
<td>59.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Clavulanate Dosed at 45 mg/kg amoxicillin 12-hourly</td>
<td>1.7</td>
<td>1.1</td>
<td>4.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

The pharmacokinetics of the two components of Co-amoxiclav (Augmentin® ES) are closely matched. 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.

**INDICATIONS**
Co-amoxiclav (Augmentin®) should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.
Co-amoxiclav (Augmentin® ES) is indicated for the short-term treatment of bacterial infections in paediatric patients at the following sites when caused by Co-amoxiclav (Augmentin®)-susceptible organisms:

Upper respiratory tract infections (including ENT) e.g.
recurrent or persistent acute otitis media due to *Streptococcus pneumoniae* (penicillin minimum inhibitory concentration (MIC) less than or equal to 4µg/ml), *Haemophilus influenzae* and *Moraxella catarrhalis*. Such
patients are often characterised by antibiotic exposure for acute otitis media within the preceding 3 months, and are either aged ≤2 years or attend daycare.

tonsillo-pharyngitis and sinusitis, typically caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*\(^\text{a}\), *Moraxella catarrhalis*\(^\text{b}\) and *Streptococcus pyogenes*.

**Lower respiratory tract infections** e.g. lobar and bronchopneumonia typically caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*\(^\text{a}\) and *Moraxella catarrhalis*\(^\text{b}\).

**Skin and soft tissue infections** typically caused by *Staphylococcus aureus*\(^\text{a}\) and *Streptococcus pyogenes*.

Other Co-amoxiclav (*Augmentin*\(^\text{®}\)) formulations are indicated for short-term treatment of bacterial infections at the following sites when caused by Co-amoxiclav (*Augmentin*\(^\text{®}\))-susceptible organisms:

**Upper respiratory tract infections** (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media typically caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*\(^\text{a}\), *Moraxella catarrhalis*\(^\text{b}\) and *Streptococcus pyogenes*.

**Lower respiratory tract infections** e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia typically caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*\(^\text{a}\) and *Moraxella catarrhalis*\(^\text{b}\).

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, female genital infections typically caused by *Enterobacteriaceae*\(^\text{a}\) (mainly *Escherichia coli*\(^\text{a}\)) *Staphylococcus saprophyticus* and *Enterococcus* species, and gonorrhoea caused by *Neisseria gonorrhoeae*\(^\text{a}\).

**Skin and soft tissue infections** typically caused by *Staphylococcus aureus*\(^\text{a}\), *Streptococcus pyogenes* and *Bacteroides* species\(^\text{a}\).

\(^{\text{a}}\)Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone (see *Pharmacological Properties, Pharmacodynamics* for further information). Susceptibility to Co-amoxiclav (*Augmentin*\(^\text{®}\)) will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

**DOSAGE AND ADMINISTRATION**

**Paediatric patients** 3 months and older:

The recommended dose for Co-amoxiclav (*Augmentin*\(^\text{®}\) ES) is 90/6.4mg/kg/day in 2 divided doses at 12-hourly intervals for 10 days (see chart below). There is no experience in paediatric patients weighing > 40kg, or in adults. There are no clinical data on Co-amoxiclav (*Augmentin*\(^\text{®}\) ES) in children under 3 months of age.
Co-amoxiclav (Augmentin® ES) does not contain the same amount of clavulanate (as the potassium salt) as any of the other Co-amoxiclav (Augmentin®) suspensions. Co-amoxiclav (Augmentin® ES) contains 42.9 mg of clavulanic acid per 5 ml whereas Co-amoxiclav (Augmentin®) 200 mg/5 ml suspension contains 28.5 mg of clavulanic acid per 5 ml and the 400 mg/5 ml suspension contains 57 mg of clavulanic acid per 5 ml. Therefore, Co-amoxiclav (Augmentin® ES) 200 mg/5 ml and 400 mg/5 ml suspensions should not be substituted for Co-amoxiclav (Augmentin® ES), as they are not interchangeable.

**Hepatic Impairment**

Dose with caution; monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation.

**Renal Impairment**

There are no dosing recommendations for Co-amoxiclav (Augmentin® ES) in patients with renal impairment.

**Method of Administration**

To minimise the potential for gastrointestinal intolerance, Co-amoxiclav (Augmentin® ES) should be taken at the start of a meal. The absorption of Co-amoxiclav (Augmentin® ES) 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. SHAKE ORAL SUSPENSION WELL BEFORE USING.

**CONTRAINDICATIONS**

Co-amoxiclav (Augmentin® ES) is contra-indicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins. Co-amoxiclav (Augmentin® ES) is contra-indicated in patients with a previous history of Co-amoxiclav (Augmentin®) - associated jaundice/hepatic dysfunction.

**WARNINGS AND PRECAUTIONS**

Before initiating therapy with Co-amoxiclav (Augmentin® ES), careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. If an allergic reaction occurs, Co-amoxiclav (Augmentin® ES) therapy should be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

Co-amoxiclav (Augmentin® ES) should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

In general Co-amoxiclav (Augmentin® ES) is well tolerated and possesses the characteristic low toxicity of the penicillin group of antibiotics. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving Co-amoxiclav (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.

Co-amoxiclav (Augmentin® ES) should be used with caution in patients with evidence of hepatic dysfunction. In patients with renal impairment, dosage of Co-amoxiclav (Augmentin®) should be adjusted according to the degree of impairment. No dosing recommendations can be made for Co-amoxiclav (Augmentin® ES) in renally impaired patients (see Dosage and Administration).

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).

Co-amoxiclav (Augmentin® ES) contains aspartame (each 5 ml of suspension contains 7 mg of phenylalanine) and so should be used with caution in patients with phenylketonuria.

**Effects on Ability to Drive and Use Machines**

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

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume of Co-amoxiclav (Augmentin® ES) providing 90/6.4 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>3.0 ml twice daily</td>
</tr>
<tr>
<td>12</td>
<td>4.5 ml twice daily</td>
</tr>
<tr>
<td>16</td>
<td>6.0 ml twice daily</td>
</tr>
<tr>
<td>20</td>
<td>7.5 ml twice daily</td>
</tr>
<tr>
<td>24</td>
<td>9.0 ml twice daily</td>
</tr>
<tr>
<td>28</td>
<td>10.5 ml twice daily</td>
</tr>
<tr>
<td>32</td>
<td>12.0 ml twice daily</td>
</tr>
<tr>
<td>36</td>
<td>13.5 ml twice daily</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Co-amoxiclav (Augmentin® ES) may result in increased and prolonged blood levels of amoxicillin but not clavulenate.

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 Co-amoxiclav (Augmentin® ES) and allopurinol.

In common with other antibiotics, Co-amoxiclav (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 Co-amoxiclav (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

Use in Pregnancy
Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered Co-amoxiclav (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 Co-amoxiclav (Augmentin®) may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Use in Lactation
Co-amoxiclav (Augmentin® ES) may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

ADVERSE 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
Common Diarrhoea, nausea, vomiting
Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking Co-amoxiclav (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)

**OVERDOSAGE AND TREATMENT**
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).

Co-amoxiclav (Augmentin® ES) can be removed from the circulation by haemodialysis.

A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

**STORAGE CONDITIONS**
The powder for oral suspension should be stored in a well sealed container, at temperatures not exceeding 30°C. Keep dry. Reconstituted suspensions should be stored in a refrigerator (2-8°C) and used within 10 days.

**INSTRUCTIONS FOR USE AND HANDLING**
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.
- 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.

Each teaspoonful (5mL) will contain 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanate as the potassium salt.

**AVAILABILITY**
Co-amoxiclav (Augmentin® ES) 600mg/42.9mg per 5mL Powder for Suspension: Bottles of 50mL and 100mL

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

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Version number: GDS21/IPI08 Revision date: 18 January 2013

Imported by: GlaxoSmithKline Philippines Inc 2286 Chino Roces Avenue, City of Makati Tel. 892-0761

Mfd. By: Glaxo Wellcome Production Mayenne, France
Co-Amoxiclav
Augmentin®
50mg/12.5mg per mL Powder for Suspension (Infant Drops)

PRODUCT DESCRIPTION
Co-amoxiclav (Augmentin®) 50mg/12.5mg per mL. Powder for Suspension (Infant Drops): Bottle of dry powder for reconstitution in water, at time of dispensing, to form an oral sugar-free suspension. Each mL of the reconstituted suspension contains 50mg amoxicillin as trihydrate and 12.5mg clavulanic acid as potassium salt.

PHARMACOLOGIC 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 Co-amoxiclav (Augmentin®) infant drops anticipates this defence mechanism by blocking the \( \beta \)-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 Co-amoxiclav (Augmentin®) it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

Co-amoxiclav (Augmentin®) is bactericidal to a wide range of organisms including:

- **Gram-positive**
  - Aerobes: Enterococcus faecalis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans,
  - Staphylococcus aureus, *coagulase negative staphylococci* (including Staphylococcus epidermidis), Corynebacterium species, Bacillus anthracis, Listeria monocytogenes.
  - Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

- **Gram-negative**
  - Anaerobes: *Bacteroides spp.*, including *B. fragilis*.

* Some members of these species of bacteria produce \( \beta \)-lactamase, rendering them insensitive to amoxicillin alone.

Pharmacokinetics
The pharmacokinetics of the two components of Co-amoxiclav (Augmentin®) are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of Co-amoxiclav (Augmentin®) is optimised at the start of a meal.

Doubling the dosage of Co-amoxiclav (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.

INDICATIONS
Co-amoxiclav (Augmentin®) infant drops are 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.

A comprehensive list of susceptible organisms is provided in the Pharmacodynamics section.

Infections caused by amoxicillin-susceptible organisms are amenable to Co-amoxiclav (Augmentin®) treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Co-amoxiclav (Augmentin®)-susceptible \( \beta \)-lactamase producing organisms may therefore be treated with Co-amoxiclav (Augmentin®).

DOSAGE AND ADMINISTRATION
The usual recommended daily dosage is 25 mg/kg/day* in divided doses every eight hours.

In more serious infections the dosage may be increased up to 50 mg/kg/day in divided doses every eight hours.

* Each 25 mg Co-amoxiclav (Augmentin®) provides 20 mg amoxicillin and 5 mg clavulante.

Co-amoxiclav (Augmentin®) infant drops should be administered using the supplied syringe doser. The syringe doser has markings which correspond to the weight of the child. For example, for a child weighing 7 kg, the syringe piston should be withdrawn until the 7 kg marking is level with the top of the body of the syringe. The dose (equivalent to 0.93 mL) should then be orally administered to the child. A similar dose should be administered once every eight hours.

For information, the volumes of Co-amoxiclav (Augmentin®) infant drops which correspond to the weight markings are shown below:

<table>
<thead>
<tr>
<th>Weight of child (kg)</th>
<th>Volume (ml) of Co-amoxiclav (Augmentin®) infant drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.09 – 1.5</td>
<td>0.15 – 0.25</td>
</tr>
<tr>
<td>1.5 – 4</td>
<td>0.25 – 0.5</td>
</tr>
<tr>
<td>4 – 6.6</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>6.6 – 9</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>9 – 12</td>
<td>1.5 – 2.0</td>
</tr>
<tr>
<td>12 – 15</td>
<td>2.0 – 2.5</td>
</tr>
</tbody>
</table>

* Some members of these species of bacteria produce \( \beta \)-lactamase, rendering them insensitive to amoxicillin alone.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.13</td>
</tr>
<tr>
<td>1.5</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.27</td>
</tr>
<tr>
<td>2.5</td>
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<td>7.5</td>
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<td>8</td>
<td>1.07</td>
</tr>
<tr>
<td>8.5</td>
<td>1.14</td>
</tr>
<tr>
<td>9</td>
<td>1.20</td>
</tr>
<tr>
<td>9.5</td>
<td>1.27</td>
</tr>
<tr>
<td>10</td>
<td>1.34</td>
</tr>
</tbody>
</table>

**These doses may be doubled in cases of severe infection.**
Dosage in renal impairment

<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, ie The recommended dose given three times daily*</td>
<td>The recommended dose given twice daily instead of three times per day*</td>
<td>The recommended dose given once daily instead of three times per day*</td>
</tr>
</tbody>
</table>

* In more serious cases this dose may be doubled.

Dosage in hepatic impairment

Dose with caution; monitor hepatic function at regular intervals.

Administration

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Co-amoxiclav (Augmentin®) is optimised when taken at the start of a meal.

Duration of therapy should be appropriate to the indication and should not be extended beyond 14 days without review.

CONTRAINDICATIONS

Co-amoxiclav (Augmentin®) is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

Co-amoxiclav (Augmentin®) is contraindicated in patients with a previous history of Co-amoxiclav (Augmentin®)-associated jaundice/hepatic dysfunction.

WARNINGS AND PRECAUTIONS

Before initiating therapy with Co-amoxiclav (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 Contraindications).

Co-amoxiclav (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 Co-amoxiclav (Augmentin®). Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Changes in liver function tests have been observed in some patients receiving Co-amoxiclav (Augmentin®). The clinical significance of these changes is uncertain but Co-amoxiclav (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 Co-amoxiclav (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).

Co-amoxiclav (Augmentin®) suspensions contain 2.5 mg aspartame per 1 mL, which is a source of phenylalanine, and therefore should be used with caution in patients with phenylketonuria.

Effects on Ability to Drive and Use Machines

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

DRUG INTERACTIONS

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin.

Concomitant use with Co-amoxiclav (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 Co-amoxiclav (Augmentin®) and allopurinol.

In common with other broad spectrum antibiotics, Co-amoxiclav (Augmentin®) may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

PREGNANCY AND LACTATION

Reproduction studies in animals (mice and rats) with orally and parenterally administered Co-amoxiclav (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 Co-amoxiclav (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.

Co-amoxiclav (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.
ADVERSE 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 (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

Common: Diarrhoea, nausea, vomiting

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking Co-amoxiclav (Augmentin®) at the start of a meal.

Uncommon: Indigestion

Very Rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Superficial tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration 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)

OVERDOSAGE AND TREATMENT

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). Co-amoxiclav (Augmentin®) may be removed from the circulation by haemodialysis.

STORAGE CONDITION

Before reconstitution, the dry powder should be stored in an unopened container in a dry place. Store below 25°C.

Reconstituted suspension should be stored in a refrigerator (2-8°C) and used within seven days.

INSTRUCTIONS FOR USE AND HANDLING

First shake the bottle to loosen the powder. Water should be added until the fill line on the bottle label, and then shake the bottle well. Then top up with water until the level of the fill line is reached and shake again. When first reconstituted, allow to stand for 5 minutes to ensure full dispersion.

The device is used to dose patients under 2 years according to the schedule in the Dosage and Administration section.
### AVAILABILITY
Co-amoxiclav *(Augmentin®)* 50mg/12.5mg per mL Powder for Suspension (Infant Drops): Type III clear glass bottle with an aluminium roll on pilfer-proof cap x 20mL (net content) + plastic syringe dosing device. Box of 1’s.

#### CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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Version number: GDS15/IPI05
Revision date: 21 April 2005

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**Shake bottle before use**  
**Insert pipette into adaptor, ensure firmly located**  
**Invert bottle and withdraw required dose**  
**Place bottle upright and remove pipette from adaptor.**  
**Rinse pipette in clean water**  
**Replace bottle cap**
Co-Amoxiclav
Augmentin®
Powder for Injection

PRODUCT DESCRIPTION
Co-Amoxiclav (Augmentin® 600) 500mg/100mg Injection: Vials of sterile powder for injection. Each vial contains 500mg amoxicillin and 100mg potassium clavulanate for reconstitution as an intravenous injection or infusion.
Co-Amoxiclav (Augmentin® 1.2) 1g/200mg Injection: Vials of sterile powder for injection. Each vial contains 1g amoxicillin and 200mg potassium clavulanate for reconstitution as an intravenous injection or infusion.

PHARMACOLOGIC 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 Co-Amoxiclav (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 Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®).
Where clinical efficacy of Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®).

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobes:</strong></td>
</tr>
<tr>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Nocardia asteroides</td>
</tr>
<tr>
<td>Streptococcus pneumoniae*</td>
</tr>
<tr>
<td>Streptococcus pyogenes*</td>
</tr>
<tr>
<td>Streptococcus agalactiae*</td>
</tr>
<tr>
<td>Viridans group streptococcus*</td>
</tr>
<tr>
<td>Streptococcus spp. (other β-hemolytic)*</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin susceptible)*</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus (methicillin susceptible)</td>
</tr>
<tr>
<td>Coagulase negative staphylococcus (methicillin susceptible)</td>
</tr>
<tr>
<td><strong>Gram-negative aerobes:</strong></td>
</tr>
<tr>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td>Leptospira icterohaemorrhagiae</td>
</tr>
<tr>
<td>Treponema pallidum</td>
</tr>
<tr>
<td><strong>Gram-positive anaerobes:</strong></td>
</tr>
<tr>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Peptococcus niger</td>
</tr>
<tr>
<td>Peptostreptococcus magnus</td>
</tr>
<tr>
<td>Peptostreptococcus micros</td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
</tr>
<tr>
<td><strong>Gram-negative anaerobes:</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
</tr>
<tr>
<td>Bacteroides spp.</td>
</tr>
<tr>
<td>Capnocytophaga spp.</td>
</tr>
<tr>
<td>Eikenella corrodens</td>
</tr>
<tr>
<td>Fusobacterium nucleatum</td>
</tr>
<tr>
<td>Fusobacterium spp.</td>
</tr>
<tr>
<td>Porphyromonas spp.</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
</tbody>
</table>

Species for which acquired resistance may be a problem
Gram-negative aerobes:
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Salmonella spp.*
- *Shigella spp.*

Gram-positive aerobes:
- *Corynebacterium spp.*
- *Enterococcus faecium*

Inherently resistant organisms
- *Acinetobacter spp.*

Gram-negative aerobes:
- *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 Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®) approximately doubles the serum levels achieved.

Pre-clinical Safety Data
No further information of relevance.

INDICATIONS
Co-Amoxiclav (Augmentin®) should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Co-Amoxiclav (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.

Co-Amoxiclav (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.

Susceptibility to Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®) treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Co-Amoxiclav (Augmentin®)-susceptible β-lactamase producing organisms may therefore be treated with Co-Amoxiclav (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 * Co-Amoxiclav (Augmentin®) eight hourly. In more serious infections, increase frequency to six-hourly intervals.

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

**Adult dosage for surgical prophylaxis**
The usual dose is 1.2 g Co-Amoxiclav (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 Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®) therapy post-operatively.

**Dosage in renal impairment**

<table>
<thead>
<tr>
<th>Adults</th>
<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. Dialysis decreases serum concentrations of Co-Amoxiclav (Augmentin®) and an additional 600 mg IV dose may need to be given during dialysis and at the end of dialysis.</td>
<td></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 Co-Amoxiclav (Augmentin®) contains 1.0 mmol of potassium and 3.1 mmol of sodium (approx.).

**Administration**
Co-Amoxiclav (Augmentin®) intravenous may be administered either by intravenous injection or by intermittent infusion. It is not suitable for intramuscular administration.

**CONTRAINDICATIONS**
Co-Amoxiclav (Augmentin®) is contra-indicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.
Co-Amoxiclav (Augmentin®) is contra-indicated in patients with a previous history of Co-Amoxiclav (Augmentin®)-associated jaundice/hepatic dysfunction.

**WARNINGS AND PRECAUTIONS**
Before initiating therapy with Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®). The clinical significance of these changes is uncertain but Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®) dosage should be adjusted as recommended in the Dosage and Administration section.
Co-Amoxiclav (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 diarrhea 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 Co-Amoxiclav (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.
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 Co-Amoxiclav (Augmentin®) may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Effects on Ability to Drive and Use Machines
Adverse effects on the ability to drive or operate machinery have not been observed.

DRUG INTERACTIONS
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Co-Amoxiclav (Augmentin®) may result in increased and prolonged blood levels of amoxicillin but not of clavulanate.

There are no data on the concomitant use of Co-Amoxiclav (Augmentin®) and allopurinol. In common with other antibiotics, Co-Amoxiclav (Augmentin®) may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. The presence of clavulanic acid in Co-Amoxiclav (Augmentin®) may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

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 Co-Amoxiclav (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.

Incompatibilities
Co-Amoxiclav (Augmentin®) intravenous should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.

If Co-Amoxiclav (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.

PREGNANCY AND LACTATION
Use in Pregnancy
Reproduction studies in animals (mice and rats) with orally and parenterally administered Co-Amoxiclav (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 Co-Amoxiclav (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
Co-Amoxiclav (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.

ADVERSE 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:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common &gt;1/10</td>
<td></td>
</tr>
<tr>
<td>Common &gt;1/100 and &lt;1/10</td>
<td></td>
</tr>
<tr>
<td>Uncommon &gt;1/1000 and &lt;1/100</td>
<td></td>
</tr>
<tr>
<td>Rare &gt;1/10,000 and &lt;1/1000</td>
<td></td>
</tr>
<tr>
<td>Very rare &lt;1/10,000</td>
<td></td>
</tr>
</tbody>
</table>

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 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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Nausea, vomiting, indigestion</td>
</tr>
<tr>
<td>Very rare</td>
<td>Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis – See Warnings and Precautions) are less likely to occur after parenteral administration.</td>
</tr>
</tbody>
</table>

Warnings and Precautions
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.
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)

OVERDOSAGE AND TREATMENT
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).
Co-Amoxiclav (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.

STORAGE CONDITION
Co-Amoxiclav (Augmentin®) vials should be stored at temperatures not exceeding 5°C.

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 or may not appear during reconstitution. Reconstituted solutions are normally
colourless or a pale, straw colour.

Intravenous injection:
The stability of Co-Amoxiclav (Augmentin®) intravenous solution is concentration dependent, thus Co-
Amoxiclav (Augmentin®) intravenous should be used immediately upon reconstitution and given by slow
intravenous injection over a period of 3-4 minutes. Co-Amoxiclav (Augmentin®) intravenous solutions should
be used within 20 minutes of reconstitution. Co-Amoxiclav (Augmentin®) may be injected directly into a vein or
via a drip tube.

Intravenous infusion:
Alternatively, Co-Amoxiclav (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 Co-Amoxiclav (Augmentin®) may be given in a range of different intravenous fluids.
Satisfactory antibiotic concentrations are retained at 5°C and at room temperature (25°C) 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 25°C</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. Co-Amoxiclav (Augmentin®) is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solutions of Co-Amoxiclav (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 5°C, 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 5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for Injections B.P.</td>
<td>8 hours</td>
</tr>
<tr>
<td>Sodium Chloride Intravenous Infusion B.P. (0.9% w/v)</td>
<td>8 hours</td>
</tr>
</tbody>
</table>

**AVAILABILITY**
Box of 10 vials

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

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Tel. 892-0761

Mfd. By:
SmithKline Beecham plc
Worthing, West Sussex, United Kingdom
**Co-Amoxiclav**

**Augmentin®**

**Oral Preparations**

**PRODUCT DESCRIPTION**

**Powder for Suspension (in bottles)**

Co-amoxiclav (Augmentin®) 156.25mg/5mL Powder for Suspension: Bottles of powder for the preparation of fruit flavoured suspension. When reconstituted, each 5mL contains 125mg amoxicillin and 31.25 clavulanic acid.

Co-amoxiclav (Augmentin®) 312.5mg/5mL Powder for Suspension: Bottles of powder for the preparation of fruit flavoured suspension. When reconstituted, each 5mL contains 250mg amoxicillin and 62.5mg clavulanic acid.

Co-amoxiclav (Augmentin®) 228.5mg/5mL Powder for Suspension: Bottles of powder for the preparation of fruit flavoured suspension. When reconstituted, each 5mL contains 200mg amoxicillin and 28.5mg clavulanic acid.

Co-amoxiclav (Augmentin®) 457mg/5mL Powder for Suspension: Bottles of powder for the preparation of strawberry flavoured suspension. When reconstituted, each 5mL contains 400mg amoxicillin and 57mg clavulanic acid.

**Tablets**

Co-amoxiclav (Augmentin®) 375mg Tablet: White, oval film-coated tablets with 'AUGMENTIN' engraved on one side. Each tablet contains 250mg amoxicillin and 125mg clavulanic acid.

Co-amoxiclav (Augmentin®) 625mg Tablet: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side. Each tablet contains 500mg amoxicillin and 125mg clavulanic acid.

Co-amoxiclav (Augmentin®) 1g Tablet: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side. Each tablet contains 875mg amoxicillin and 125mg clavulanic acid.

Co-amoxiclav (beta-lactam antibacterial penicillin coformulated with a beta-lactamase inhibitor) 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 amoxicillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics.

**PHARMACOLOGIC PROPERTIES**

**Pharmacodynamics**

**Mechanism of Action**

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by beta-lactamasases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes. Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.

The presence of clavulanic acid in co-amoxiclav formulations protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus amoxicillin-clavulanate possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

**Pharmacodynamic Effects**

In the list below, organisms are categorised according to their in vitro susceptibility to amoxicillin-clavulanate.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobes:</strong></td>
</tr>
<tr>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Nocardia asteroides</td>
</tr>
<tr>
<td>Streptococcus pyogenes&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Streptococcus agalactiae&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Streptococcus spp. (other β-hemolytic) &lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin susceptible)*</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus (methicillin susceptible)</td>
</tr>
<tr>
<td>Coagulase negative staphylococci (methicillin susceptible)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gram-negative aerobes:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Vibrio cholera</td>
</tr>
</tbody>
</table>
Other:
Borrelia burgdorferi
Leptospira icterohaemorrhagiae
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

Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Hafnia alvei
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas spp.
Serratia spp.
Stenotrophomas maltophilia
Versinia enterolitica

Others:
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia spp.
Coxiella burnetti
Mycoplasma spp.

Pharmacokinetics

Absorption
The two components of co-amoxiclav, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.

The pharmacokinetic results for two separate studies, in which co-amoxiclav 250/125 (375) or 2 x 250/125 and 500/125 (625) mg tablets (in comparison with the two components given separately) were administered in the fasting state to groups of healthy volunteers, are presented below.

![Mean pharmacokinetic parameters](image)
Amoxicillin 500 mg | 500 | 6.5 | 1.3 | 19.5 | 1.1
---|---|---|---|---|---
Co-amoxiclav 250/125 mg | 125 | 2.2 | 1.2 | 6.2 | 1.2
Co-amoxiclav 500/125 mg | 125 | 2.8 | 1.3 | 7.3 | 0.8
Clavulanic acid 125 mg | 125 | 3.4 | 0.9 | 7.8 | 0.7
Co-amoxiclav 250/125 mg x 2 | 250 | 4.1 | 1.3 | 11.8 | 1.0

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

**Distribution**
Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein.

From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

**Metabolism**
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

**Elimination**
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms.

Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 250/125 mg or a single 500/125 mg tablet. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions).

**INDICATIONS**
Amoxicillin-clavulanate should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

**Adult formulations:**
Co-amoxiclav is indicated for short term treatment of bacterial infections at the following sites when caused by amoxicillin-clavulanate-susceptible organisms:
- Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media, typically caused by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.
- Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia, typically caused by Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.
- Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, female genital infections typically caused by Enterobacteriaceae (mainly Escherichia coli), Staphylococcus saprophyticus and Enterococcus species and gonorrhoea caused by Neisseria gonorrhoeae.
- Skin and soft tissue infections typically caused by Staphylococcus aureus, Streptococcus pyogenes and Bacteroides species.
- Bone and joint infections e.g. osteomyelitis typically caused by Staphylococcus aureus, where more prolonged therapy may be appropriate.
- Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

**Paediatric formulations:**
Co-amoxiclav is indicated for short term treatment of bacterial infections at the following sites when caused by amoxicillin-clavulanate sensitive organisms:
- Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media typically caused by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.
- Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia typically caused by Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.
- Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis, female genital infections typically caused by Enterobacteriaceae (mainly Escherichia coli), Staphylococcus saprophyticus and Enterococcus species, and gonorrhoea caused by Neisseria gonorrhoeae.
- Skin and soft tissue infections typically caused by Staphylococcus aureus, Streptococcus pyogenes and Bacteroides species.

Amoxicillin-clavulanate Paediatric three times daily.
The paediatric three times daily dosing regimen is also indicated for the following infections:
- Bone and joint infections e.g. osteomyelitis typically caused by *Staphylococcus aureus*, where more prolonged therapy may be appropriate.
- Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

**All formulations:**

Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone. (see Clinical Pharmacology, Pharmacodynamic effects for further information).

Susceptibility to amoxicillin-clavulanate will vary with geography and time. 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 co-amoxiclav treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with amoxicillin-clavulanate-susceptible beta-lactamase-producing organisms may therefore be treated by co-amoxiclav.

**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 co-amoxiclav 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 co-amoxiclav 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.

**Populations**

- **Adults**

| Mild to moderate infections | 250/125 mg given 3 times daily, OR 500/125 mg given 2 or 3 times daily, OR 875/125 mg given twice daily |
| Severe infections (including chronic and recurrent urinary tract infections and those of the lower respiratory tract) | 2 times 250/125 mg given 3 times daily, OR 1 to 2 times 500/125 mg given 3 times daily, OR 875/125 mg given 2 or 3 times daily |

Two co-amoxiclav 250/125 mg tablets should not be substituted for one co-amoxiclav 500/125 mg tablet since they are not equivalent.

- **Children**

Dosage should be expressed in terms of the age of the child and either in mg/kg/day (given in 2 or 3 divided doses) or ml of suspension per dose or equivalent for other presentations.

Children weighing 40 kg and over should be dosed according to the adult recommendations.

**Children up to 12 years**

<table>
<thead>
<tr>
<th>Lower dose (mg/kg/day)</th>
<th>Three times daily (4:1) formulations</th>
<th>Twice daily (7:1) formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/5 to 40/10</td>
<td>25/3.6 to 45/6.4</td>
<td></td>
</tr>
<tr>
<td>40/10 to 60/15</td>
<td>45/6.4 to 70/10</td>
<td></td>
</tr>
</tbody>
</table>

The lower dose is recommended for infections such as skin and soft tissue and recurrent tonsilitis.

The higher dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections.

No clinical data are available on doses of these formulations higher than 40/10 mg/kg/day (4:1) or 45/6.4 mg/kg/day (7:1) in children under 2 years.

There are no clinical data for the 7:1 formulation for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

The 8:1 ratio formulation is recommended for dosing at 40/5 to 80/10 mg/kg/day (in three divided doses) in children aged 1 to 30 months, depending upon severity of infection.

**Premature**

No dosage recommendation can be made for this category.

- **Elderly**

No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

- **Renal impairment**

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

**Adults:**

| Creatinine clearance greater than 30 ml/min | No adjustment necessary. |
| Creatinine clearance 10 to 30 ml/min | 1 times 500/125 mg given twice daily; OR 1 to 2 times 250/125 mg, depending upon severity of infection, given twice daily (*) |
| Creatinine clearance less than 10 ml/min | 1 times 500/125 mg given once daily OR 1 to 2 times 250/125 mg; depending upon severity of infection, given once daily(“) |

(+ The 875/125 mg and 1000/125 mg presentations should only be used in patients with a creatinine clearance of more than 30 ml/min.

**Children:**

| Creatinine clearance greater than 30 ml/min: | No adjustment necessary. |
| Creatinine clearance 10 to 30 ml/min: | 15/3.75 mg/kg given twice daily (maximum 500/125 mg twice daily). |
| Creatinine clearance less than 10 ml/min: | 15/3.75 mg/kg given as a single daily dose (maximum 500/125 mg). |
In the majority of cases, parenteral therapy, where available, may be preferred.

**Haemodialysis**

**Adults:**

1 times 500/125 mg OR 2 times 250/125 mg every 24 hours, **PLUS** 1 dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased) (*)

(+) The 875/125 mg and 1000/125 mg presentations should only be used in patients with a creatinine clearance of more than 30 ml/min.

**Children:**

15/3.75 mg/kg/day given as a single daily dose.

Prior to haemodialysis one additional dose of 15/3.75 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15/3.75 mg/kg should be administered after haemodialysis.

- **Hepatic impairment**
  - Dose with caution; monitor hepatic function at regular intervals.
  - There are insufficient data on which to base a dosage recommendation.

### CONTRAINDICATIONS

- Co-amoxiclav is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and 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. If an allergic reaction occurs, co-amoxiclav therapy should be discontinued and appropriate alternative therapy instituted.
- Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, i.v. steroids and airway management, including intubation may also be required.
- Co-amoxiclav should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.
- Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.
- Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.
- In general co-amoxiclav is well tolerated and possesses the characteristic low toxicity of the penicillin group of antibiotics. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.
- Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

- Co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.
- In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration - Renal impairment).
- In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Overdosage).

- Co-amoxiclav Suspensions/Sachets/Chewable Tablets (where applicable), contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

### WARNINGS AND PRECAUTIONS

Before initiating therapy with co-amoxiclav, 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. If an allergic reaction occurs, co-amoxiclav therapy should be discontinued and appropriate alternative therapy instituted.

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### ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

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

### DRUG INTERACTIONS

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin-clavulanate may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Co-administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol. In common with other antibiotics, co-amoxiclav may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.
PREGNANCY AND LACTATION

Pregnancy
Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered co-amoxiclav 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 co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Lactation
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

ADVERSE EFFECTS

Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency. The following convention has been used for the classification of frequency:

- very common >1/10
- common >1/100 and <1/10
- uncommon >1/1000 and <1/100
- rare >1/10,000 and <1/1000
- very rare <1/10,000.

Infections and infestations

- Common: Mucocutaneous candidiasis
- 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 co-amoxiclav at the start of a meal.

- Uncommon: Indigestion
- Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). (See Warnings and Precautions)
- Rare: Black hairy tongue
- Very rare: Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

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

Hepatobiliary disorders

- Uncommon: A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
- Very rare: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

Children (additional statement):
These events have been very rarely reported in children.

**All populations:**
Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Skin and subcutaneous tissue disorders

- Uncommon: Skin rash, pruritus, urticaria
- Rare: Erythema multiforme
- Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP)

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

Renal and urinary disorders
Very rare

Interstitial nephritis, crystalluria (see Overdosage)

OVERDOSAGE AND TREATMENT

Symptoms and Signs
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.
Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Warnings and Precautions).

TREATMENT
GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance.
Co-amoxiclav can be removed from the circulation by haemodialysis

Children (additional statement):
A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Drug abuse and dependence
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

STORAGE CONDITIONS
Co-amoxiclav tablet should be stored at temperatures not exceeding 25ºC. Keep dry.
Co-amoxiclav powder for suspension should be stored at temperatures not exceeding 25ºC.
The reconstituted suspension should be stored and kept in a refrigerator (2-8 ºC) and used within 7 to 10 (maximum days). Do not freeze.

INSTRUCTIONS FOR USE AND HANDLING
For sachet, contents should be stirred into water before taking.
For administration of suspensions to children below 3 months, a syringe graduated to permit accurate and reproducible volumes to be dispensed, should be used.
For administration to children up to 2 years old, co-amoxiclav suspensions may be diluted to half-strength using water.

AVAILABILITY

Powder for Suspension (in bottles)
* Co-amoxiclav (Augmentin®) 156.25 mg/5mL Powder for Suspension: Bottles of 60mL
* Co-amoxiclav (Augmentin®) 312.5mg/5mL Powder for Suspension: Bottles of 60mL
** Co-amoxiclav (Augmentin®) 228.5mg/5mL Powder for Suspension: Bottles of 70mL
** Co-amoxiclav (Augmentin®) 457mg/5mL Powder for Suspension: Bottles of 35mL and 70mL
** Co-amoxiclav (Augmentin®) 625mg Tablet: 10 tablets per blister (Box of 30’s), foil-wrapped.
** Co-amoxiclav (Augmentin®) 1g Tablet: 7 tablets per blister (Box 14 tablets), foil-wrapped.

Tablets
** Co-amoxiclav (Augmentin®) 375mg Tablet: 10 tablets per blister (Box of 30’s), foil-wrapped.
** Co-amoxiclav (Augmentin®) 625mg Tablet: 10 tablets per blister (Box of 30’s), foil-wrapped.
** Co-amoxiclav (Augmentin®) 1g Tablet: 7 tablets per blister (Box 14 tablets), foil-wrapped.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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GlaxoSmithKline

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