

DATA SHEET

AUGMENTIN[®] ES

Amoxicillin trihydrate/potassium clavulanate

Presentation

AUGMENTIN ES (extra strength) dry powder for oral suspension:

Each 5mL of reconstituted suspension contains 600mg amoxicillin (as the trihydrate) and 42.9mg clavulanic acid (as the potassium salt) in a ratio of 14:1.

Uses

Actions

Pharmacotherapeutic group: Antibacterial

AUGMENTIN ES (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.

Pharmacodynamic properties

Microbiology: 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-lactamases 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 **AUGMENTIN** 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 **AUGMENTIN** possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

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

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***In vitro* susceptibility of micro-organisms to amoxicillin-clavulanate**

Where clinical efficacy of amoxicillin-clavulanate 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 amoxicillin-clavulanate.

Commonly susceptible species

Gram-positive aerobes:

Bacillus anthracis

Enterococcus faecalis

Listeria monocytogenes

Nocardia asteroides

Streptococcus pneumoniae^{*†}

Streptococcus pyogenes^{*†}

Streptococcus agalactiae^{*†}

Viridans group streptococcus[†]

Streptococcus spp. (other β-hemolytic) ^{*†}

Staphylococcus aureus (methicillin susceptible)^{*}

Staphylococcus saprophyticus (methicillin susceptible)

Coagulase negative staphylococcus (methicillin susceptible)

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Gram-negative aerobes:

Bordetella pertussis

*Haemophilus influenzae**

Haemophilus parainfluenzae

Helicobacter pylori

*Moraxella catarrhalis**

Neisseria gonorrhoeae

Pasteurella multocida

Vibrio cholerae

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.

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Species for which acquired resistance may be a problem
<u>Gram-negative aerobes:</u> <i>Escherichia coli</i> * <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> * <i>Klebsiella</i> spp. <i>Proteus mirabilis</i> <i>Proteus vulgaris</i> <i>Proteus</i> spp. <i>Salmonella</i> spp. <i>Shigella</i> spp.
<u>Gram-positive aerobes:</u> <i>Corynebacterium</i> spp. <i>Enterococcus faecium</i>
Inherently resistant organisms
<u>Gram-negative aerobes:</u> <i>Acinetobacter</i> spp. <i>Citrobacter freundii</i> <i>Enterobacter</i> spp. <i>Hafnia alvei</i> <i>Legionella pneumophila</i> <i>Morganella morganii</i> <i>Providencia</i> spp. <i>Pseudomonas</i> spp. <i>Serratia</i> spp. <i>Stenotrophomas maltophilia</i>

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Yersinia enterocolitica

Others:

Chlamydia pneumoniae

Chlamydia psittaci

Chlamydia spp.

Coxiella burnetii

Mycoplasma spp.

Pharmacokinetic properties

Absorption: The two components, of **AUGMENTIN ES**, 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 **AUGMENTIN ES** is enhanced when taken at the start of a meal.

Pharmacokinetics: Pharmacokinetic parameters are given below for **AUGMENTIN ES** administered at 45mg/kg every 12 hours to paediatric patients

Formulation	C _{max} (mg/L)	t _{max} (hours)	AUC (mg.h/L)	t _{1/2} (hours)
Augmentin ES 600/42.9mg/5mL (14:1) Dosed at 45mg/kg amoxicillin 12-hourly	<i>Amoxicillin</i>			
	15.7	2.0	59.8	1.4
	<i>Clavulanic acid</i>			
	1.7	1.1	4.0	1.1

The pharmacokinetics of amoxicillin following oral administration of **AUGMENTIN ES** are similar to those observed following oral administration of amoxicillin alone.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions).

Distribution: Following intravenous 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

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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.

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 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250/125mg or a single 500/125mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% 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.

Indications

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

AUGMENTIN ES is indicated for short-term treatment of bacterial infections at the following sites when caused by **AUGMENTIN**-sensitive organisms:

- Upper Respiratory Tract Infections (including ENT) e.g. Recurrent or persistent acute otitis media due to *Streptococcus pneumoniae* (penicillin minimum inhibitory concentration (MIC) $\leq 4\mu\text{g/mL}$), *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**, *Moraxella catarrhalis** and *Streptococcus pyogenes*.

- Lower Respiratory Tract Infections e.g. lobar and bronchopneumonia typically caused by *Streptococcus pneumoniae*, *Haemophilus influenzae** and *Moraxella catarrhalis**.
- Skin and Soft Tissue Infections typically caused by *Staphylococcus aureus** and *Streptococcus pyogenes*.

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

Susceptibility to **AUGMENTIN** 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

Dosage

Children up to 12 years

AUGMENTIN ES is recommended for dosing at 90/6.4mg/kg/day in two divided doses at 12-hourly intervals for 10 days, in children aged 3 months and older.

There is no experience in paediatric patients weighing >40kg.

There are no clinical data on **AUGMENTIN ES** in children under 3 months of age.

Adults

There is no experience with Augmentin ES in adults.

AUGMENTIN ES does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other **AUGMENTIN** suspensions. **AUGMENTIN ES** (600mg/5mL) contains 42.9mg of clavulanic acid per 5mL whereas **AUGMENTIN 125** (125mg/5mL) suspension contains 31.25 mg of clavulanic acid per 5mL and **AUGMENTIN FORTE 250** (250mg/5mL) suspension contains 62.5mg of clavulanic acid per 5mL. Therefore, the **AUGMENTIN** 125mg/5mL and 250mg/5mL suspensions should not be substituted for **AUGMENTIN ES** (600 mg/5mL), as they are not interchangeable.

Renal Impairment

There are no dosage recommendations for AUGMENTIN ES in children with renal impairment.

In children with renal impairment, dosage should be adjusted according to degree of impairment using the alternative AUGMENTIN (4:1 ratio) 125mg/31.25mg or 250mg/62.5mg formulations.

Administration

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of **AUGMENTIN** is optimised when taken at the start of a meal. Treatment should not be extended beyond 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

Contraindications

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

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

Warnings and Precautions

Before initiating therapy with **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, **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.

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 occasionally result in overgrowth of non-susceptible organisms.

In general **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 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.

AUGMENTIN ES should be used with caution in patients with evidence of hepatic dysfunction.

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.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

The occurrence at treatment initiation of a feverish generalised erythema associated with pustule may be a symptom of acute generalised exanthemous pustulosis

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(AEGP). This reaction requires AUGMENTIN discontinuation and is a contraindication to subsequent administration of amoxicillin.

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

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.

AUGMENTIN ES contains aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria. Each 5mL of **AUGMENTIN ES** suspension contains 7mg of phenylalanine.

Use during 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 **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, unless considered essential by the physician.

Use in Lactation: **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.

Effects on the ability to drive and operate machinery

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

Adverse Effects

Data from large clinical trials with **AUGMENTIN ES** and other **AUGMENTIN** formulations 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 $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ 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

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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 **AUGMENTIN** at the start of a meal.

Uncommon Indigestion

Very Rare Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).

Black hairy tongue.

Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Hepatobiliary disorders:

Uncommon A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown

Very Rare Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.
(see Warnings and Precautions)

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

Interactions

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

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

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In common with other antibiotics, **AUGMENTIN** may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

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

Overdosage

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

Augmentin can be removed from the circulation by haemodialysis.

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

AUGMENTIN can be removed from the circulation by haemodialysis.

A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250mg/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 **AUGMENTIN**.

Pharmaceutical Precautions

Instructions for Use/Handling

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

Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Augmentin ES	
Bottle Size (mL)	Amount of Water Required for Suspension (mL)
50	50
75	70

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100	90
150	135

Each 5mL of reconstituted suspension contains 600mg amoxicillin as the trihydrate and 42.9mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

For administration to children up to 2 years old, **AUGMENTIN** suspensions may be diluted to half-strength using water.

Shelf life

Dry powder: 24 months

Reconstituted suspension: After reconstitution use for up to 10 days (maximum).

Special storage precautions

Dry powder: Do not store above 25°C. Keep the container tightly closed.

Reconstituted suspension: Once reconstituted, store at 2°C to 8°C. Do not freeze. Keep the container tightly closed.

As with all other **AUGMENTIN** preparations, **AUGMENTIN ES**, should be stored in unopened well sealed original packs in a dry place at less than 25°C. Keep out of reach of children.

Medicine Classification

Prescription Medicine.

Package Quantities

Clear glass bottles (Type III) closed with an aluminium closure with PVC liner. A measuring cup is provided in each pack.

Bottle sizes of 50mL, 75mL, 100mL and 150mL. The bottle pack is placed in a cardboard carton.

Further Information

List of excipients:

Aspartame
Carmellose sodium
Artificial Strawberry Cream Flavour
Silicon
Silicon dioxide
Xanthum gum

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