AUGMENTIN ES

Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Off-white powder which, when reconstituted, yields an off-white to tan coloured, strawberry flavoured suspension.

When reconstituted each 5mL contains 600 mg amoxicillin (as amoxicillin trihydrate) and 42.9 mg clavulanic acid (as potassium clavulanate), a 14:1 ratio.

CLINICAL INFORMATION

Indications

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

AUGMENTIN ES is indicated for the treatment of paediatric patients with acute otitis media due to *Streptococcus pneumoniae* (penicillin minimum inhibitory concentration (MIC) less than or equal to $\leq$ 2 μg/mL), *Haemophilus influenzae* (including beta-lactamase producing strains) and *Moraxella catarrhalis* (including beta-lactamase producing strains). Such patients are often characterised by antibiotic exposure for acute otitis media within the preceding 3 months, and are either aged $\leq$ 2 years or attend daycare.

Susceptibility to *AUGMENTIN ES* 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

Pharmaceutical form: Powder for oral suspension.

Paediatric patients 3 months and older:

The recommended dose for *AUGMENTIN ES* is 90/6.4 mg/kg/day in 2 divided doses at 12-hourly intervals for 10 days (see chart below). There is no experience in paediatric patients weighing more than 40 kg, or in adults. There are no clinical data on *AUGMENTIN ES* in children under 3 months of age.

Body Weight (kg)	**Volume of *AUGMENTIN ES* providing 90/6.4 mg/kg/day**

8	3.0 mL twice daily
12	4.5 mL twice daily
16	6.0 mL twice daily
20	7.5 mL twice daily
24	9.0 mL twice daily
28	10.5 mL twice daily
32	12.0 mL twice daily
36	13.5 mL twice daily

AUGMENTIN ES does not contain the same amount of clavulanate (as the potassium salt) as any of the other *AUGMENTIN* suspensions. *AUGMENTIN ES* contains 42.9 mg of clavulanate per 5 mL whereas *AUGMENTIN* 200 mg/5 mL suspension contains 28.5 mg of clavulanate per 5 mL and the 400 mg/5 mL suspension contains 57 mg of clavulanate per 5 mL. Therefore, *AUGMENTIN* 200 mg/5 mL and 400 mg/5 mL suspensions should not be substituted for *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 *AUGMENTIN ES* in patients with renal impairment.

Method of Administration

To minimise the potential for gastrointestinal intolerance, *AUGMENTIN ES* should be taken at the start of a meal. The absorption of *AUGMENTIN* is optimised when taken at the start of a meal.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

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 reactions (including anaphylactoid and severe cutaneous adverse 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*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to *AUGMENTIN ES* (see *Adverse Reactions*). If an allergic reaction occurs, *AUGMENTIN ES* therapy should be discontinued and appropriate alternative therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management, including intubation may also be required.

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.

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.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving *AUGMENTIN* and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.
Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

AUGMENTIN ES should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On extremely rare occasions, deaths have been reported. These have generally been cases associated with serious underlying disease or concomitant medications.

In patients with renal impairment, dosage of *AUGMENTIN* should be adjusted according to the degree of impairment. No dosing recommendations can be made for *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*).

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.

Interactions

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

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

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

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of *AUGMENTIN.*
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following the 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 *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.

Lactation

Ampicillin-class antibiotics are excreted in human milk; therefore caution should be exercised when *AUGMENTIN* is administered to a nursing mother. However, *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 Ability to Drive and Use Machines

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

Adverse Reactions

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

The following convention has been used for the classification of frequency:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥1/10,000 to <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, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very rare	Kounis syndrome (see *Warnings and Precautions*).

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 – see *Warnings and Precautions*). 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. Black Hairy Tongue

Hepatobiliary disorders

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

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

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

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very Rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).

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

Renal and urinary disorders

Very rare Interstitial nephritis, crystalluria *(*see *Overdose*)

Overdose

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

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

AUGMENTIN 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Anatomical Therapeutic Chemical (ATC) code: J01CR02.
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

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-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 microorganisms 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 clavulanate component in *AUGMENTIN ES* 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 ES* 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 *AUGMENTIN*.

In vitro* susceptibility of micro-organisms to *AUGMENTIN
Where clinical efficacy of *AUGMENTIN* has been demonstrated in clinical trials this is indicated with an asterisk (*). Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxicillin, it can be considered susceptible to *AUGMENTIN*.
Commonly susceptible species
Gram-positive aerobes: *Bacillus anthracis* *Enterococcus faecalis* *Listeria monocytogenes* *Streptococcus pneumoniae*†* *Streptococcus pyogenes*†* *Streptococcus agalactiae*†* *Viridans group streptococcus*† *Streptococcus spp. (other beta-haemolytic)*†* *Staphylococcus aureus (methicillin susceptible)** *Staphylococcus saprophyticus (methicillin susceptible)* *Coagulase negative staphylococcus (methicillin susceptible)*
Gram-negative aerobes: *Bordetella pertussis* *Haemophilus influenzae** *Helicobacter pylori*

*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae
Gram-positive anaerobes:
Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides spp.
Fusobacterium nucleatum
Fusobacterium 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.
Stenotrophomonas maltophilia

Yersinia enterocolitica
Others: *Chlamydia pneumoniae* *Chlamydia psittaci* *Chlamydia spp.* *Coxiella burnetii* *Mycoplasma spp.*

Pharmacokinetics

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

Formulation	**C max (mg/L)**	**T max (hours)**	**AUC (mg.h/L)**	**T ½ (hours)**
AUGMENTIN ES 600/42.9 mg/5mL Dosed at 45 mg/kg amoxicillin 12-hourly	***Amoxicillin***			
	15.7	2.0	59.8	1.4
	Clavulanate			
	1.7	1.1	4.0	1.1

The pharmacokinetics of the two components of *AUGMENTIN ES* are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Non-Clinical Information

No further information of relevance.

PHARMACEUTICAL INFORMATION

List of Excipients

AUGMENTIN ES powder for suspension contains colloidal silicon dioxide, sodium carboxymethylcellulose-12, strawberry cream flavour, xanthan gum, aspartame, and silicon dioxide.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are indicated on the packaging.

Do not take after the expiry date shown on the pack.

Store in a dry place in the original package to protect from moisture.

Once reconstituted, *AUGMENTIN ES* suspension must be stored in a refrigerator (2°C to 8°C) and used within 10 days. Do not freeze. (see also Use and Handling).

Nature and Contents of Container

AUGMENTIN ES powder for oral suspension is supplied in clear glass bottles containing dry powder for reconstitution. Bottles may be supplied with either an aluminium screw cap with a ring seal or a plastic child-resistant cap with a removable foil-backed seal on the bottle. Fill-lines are indicated on the bottle label. Bottles may be supplied with a plastic dosing device.

Not all presentations are available in every market.

Incompatibilities

None known.

Use and Handling

For bottles with aluminum screw caps, check the cap seal is intact before using. Alternatively, for bottles with a plastic child-resistant cap, check the foil-backed bottle seal is intact before using.

At time of use, 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.

Bottle Size (mL)	Amount of Water Required for Suspension (mL)
50	50
75	70
100	90
150	135

A dosing device may be supplied with the pack, which can be used to measure the dose accurately.

Discard unused suspension after 10 days.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

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