AUGMENTIN 625 mg

Strength

500mg/ 125mg

Pharmaceutical Dosage Form

Film-Coated debossed tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 625 mg tablets: A white to off-white oval-shaped film-coated tablet, debossed with 'AC' and a score line on one side and plain on the other side.

Each tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

CLINICAL INFORMATION

Indications

AUGMENTIN is an antibiotic agent with a notably broad-spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The 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.

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

AUGMENTIN oral presentations for three times daily dosing, 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 obstructive pulmonary disease (AECOPD)/acute exacerbation of chronic bronchitis (AECB), lobar and bronchopneumonia.

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections, e.g. boils, abscesses, cellulitis, wound infections.

Bone and joint infections e.g. osteomyelitis.

Dental infections e.g. dentoalveolar abscess.

Other infections e.g. intra-abdominal sepsis.

Susceptibility to *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 *AUGMENTIN*

treatment due to its amoxicillin content. Mixed infections caused by amoxicillin - susceptible organisms in conjunction with *AUGMENTIN* -susceptible beta-lactamase producing organisms may therefore be treated with *AUGMENTIN*.

Dosage and Administration

Pharmaceutical form: Film-coated tablet

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 amoxicillin/clavulanate 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 *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.

AUGMENTIN suspensions may be supplied with a plastic dosing device. For preparation of the suspensions see *Use and Handling*.

Adults and Children over 12 years

AUGMENTIN 625 mg tablets are not recommended in children of 12 years and under.

The usual recommended daily is:

Severe infections	One *AUGMENTIN* 625 mg tablet every 8 hours..

Renal Impairment

Adults
Dosage adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

CrCl 10-30 mL/min	The usual recommended dose of AUGMENTIN 625 mg tablets given every 12 hours.
CrCl < 10 mL/min	The usual recommended dose of AUGMENTIN 625 mg tablets given every 24 hours.
Haemodialysis	The usual recommended dose of AUGMENTIN 625 mg tablets given every 24 hours, plus a further dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).

Hepatic Impairment
Administer with caution; monitor hepatic function at regular intervals.

Contraindications

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

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

Warnings and Precautions

Before initiating therapy with *AUGMENTIN*, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Serious and occasionally fatal hypersensitivity 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* (see *Adverse Reactions*). Drug-induced enterocolitis syndrome has been reported mainly in children receiving *AUGMENTIN* (see *Adverse Reactions*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, *AUGMENTIN* 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.

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 diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

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

Changes in liver function tests have been observed in some patients receiving *AUGMENTIN*. The clinical significance of these changes is uncertain but *AUGMENTIN* should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported

rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment *AUGMENTIN* dosage should be adjusted as recommended in the *Dosage and Administration* section.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria *(*see *Overdose).*

AUGMENTIN suspensions contain 12.5 mg aspartame per 5 ml dose, which is a source of phenylalanine and 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* 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.

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 commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Pregnancy and Lactation

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 pre- term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with *AUGMENTIN* may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

AUGMENTIN may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no 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 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 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 (see *Warnings and Precautions*), serum sickness-like syndrome, hypersensitivity vasculitis (see also *Skin and subcutaneous tissue disorders).*

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

Adults

Very common	Diarrhoea
Common	Nausea, vomiting

All populations

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking *AUGMENTIN* at the start of a meal.

Uncommon	Indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), drug-induced enterocolitis syndrome (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), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also *Immune system disorders*). If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease.

Renal and urinary disorders

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

Overdose

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

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

AUGMENTIN can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code: J01CR02.

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in *AUGMENTIN* anticipates this defence mechanism by blocking the beta-lactamase enzymes, thus rendering the organisms susceptible to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as *AUGMENTIN* it produces an antibiotic agent of broad-spectrum with wide application in hospital and general practice.

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
<u>Gram-positive aerobes:</u> *Bacillius anthracis* *Enterococcus faecalis* *Listeria monocytogenes* *Nocardia asteroides* *Streptococcus pyogenes**† *Streptococcus agalactiae**† *Streptococcus* spp. (other beta-hemolytic) *† *Staphylococcus aureus* (methicillin susceptible)* *Staphylococcus saprophyticus* (methicillin susceptible) Coagulase negative staphylococcus (methicillin susceptible)
<u>Gram-negative aerobes:</u> *Bordetella pertussis* *Haemophilus influenzae** *Haemophilus parainfluenzae* *Helicobacter pylori*

*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae
Other:
Borrelia burgdorferi
Leptospira ictterohaemorrhagiae
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
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

The pharmacokinetics of the two components of *AUGMENTIN* are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of *AUGMENTIN* is optimised at the start of a meal.

Doubling the dosage of *AUGMENTIN* approximately doubles the serum levels achieved.

Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Non-Clinical Information

No further information of relevance.

PHARMACEUTICAL INFORMATION

List of Excipients

AUGMENTIN 625 mg tablets contain magnesium stearate, sodium starch glycollate, colloidal silica, microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol and dimeticone (silicone oil).

For important information about some of these excipients *see Warnings and Precautions.*

AUGMENTIN presentations do not contain sucrose, tartrazine or any other azo dyes.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

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

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

Nature and Contents of Container

Tablets are supplied in a carton containing blister packs.

Each blister pack is stored within a sealed pouch, with a desiccant sachet.

Incompatibilities

None known.

Use and Handling

Blister pouches contains a desiccant sachet; do not remove or eat. Discard any opened and unused tablets after storing as directed on the packaging.

Manufactured by

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