AUGMENTIN SR TABLETS

Amoxicillin trihydrate - Amoxicillin sodium - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN SR 1062.5 mg tablets: Each tablet contains 1000 mg amoxicillin (562.5 mg as amoxicillin trihydrate and 437.5 mg as amoxicillin sodium), and 62.5 mg clavulanic acid (as potassium clavulanate), a 16:1 ratio.

PHARMACEUTICAL FORM

White capsule shaped film coated tablets debossed with AC 1000/62.5 on one side with a bisect on the other.

CLINICAL PARTICULARS

Indications

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

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

Respiratory tract infections, e.g. community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis, typically caused *by Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* - PRSP*), Haemophilus influenzae*[#]*, Moraxella catarrhalis*[#] and *Streptococcus pyogenes*.

([#]Some members of these species of bacteria produce beta-lactamase, rendering them non-susceptible to amoxicillin alone; see *Pharmacological Properties, Pharmacodynamics* section for further information).

Susceptibility to *AUGMENTIN SR* 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 *AUGMENTIN SR* treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with *AUGMENTIN*-susceptible beta-lactamase-producing organisms may therefore by treated by *AUGMENTIN SR*. *AUGMENTIN SR* has been shown to be effective against strains of *S. pneumoniae* resistant to penicillin

(penicillin minimum inhibitory concentration (MIC) greater than or equal to 2 mg/l) (see *Pharmacodynamics* section).

Dosage and Administration

AUGMENTIN SR is indicated for use in adults greater than or equal to 16 years only.

AUGMENTIN SR tablets have a scored breakline to allow the tablet to be broken into 2 halves for ease of swallowing. This is not intended to reduce the dose of medication: both halves must be taken at the same time. The recommended dose of *AUGMENTIN SR* is 2 tablets twice a day.

***Adults*:**

Respiratory tract infections: 2 tablets twice daily for 7 to 10 days, including:

Community acquired pneumonia	2 tablets twice daily for 7 to 10 days
Acute exacerbations of chronic bronchitis	2 tablets twice daily for 7 days
Acute bacterial sinusitis	2 tablets twice daily for 10 days

Renal Impairment:

No adjustment in dosage is required in patients with creatinine clearancegreater than or equal to 30 ml/min.

AUGMENTIN SR is not recommended in patients with creatinine clearance less than 30 ml/min.

Haemodialysis

AUGMENTIN SR is not recommended in haemodialysis patients

Hepatic Impairment:

Dose with caution; monitor hepatic function at regular intervals.

There are insufficient data on which to base a dosage recommendation.

Elderly:

No adjustment needed.

Method of administration:

Oral route

Administer *AUGMENTIN SR* at the start of a meal to optimise absorption.

Treatment should not be extended beyond 14 days without review.

Contraindications

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

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

Warnings and Precautions

Before initiating therapy with *AUGMENTIN SR*, 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*). If an allergic reaction occurs, *AUGMENTIN SR* therapy must 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 SR 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.

No adjustment in *AUGMENTIN SR* dosage is required in patients with creatinine clearance greater than or equal to 30 ml/min. *AUGMENTIN SR* is not recommended in patients with creatinine clearance less than 30 ml/min.

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

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 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* 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.

Pregnancy and Lactation

Reproduction studies in animals (mice and rats) with orally and parenterally administered *AUGMENTIN* have shown no teratogenic effects. In a single study in women with 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 detrimental effects for the infant.

Effects on Ability to Drive and Use Machines

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

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 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	Genital monialiasis, 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, convulsions

Gastrointestinal disorders

Very common	Diarrhoea
Common	Nausea, abdominal pain
Uncommon	Vomiting, indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis – see Warnings and Precautions), 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.

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), 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 (GI) symptoms and disturbance of the fluid and electrolyte balances may be evident. GI 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.

Drug abuse and dependence

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Microbiology:
Amoxicillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. 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.

Clavulanate 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 clavulanate in *AUGMENTIN SR* 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 SR* 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 *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: *Bacillius 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)
Gram-negative aerobes: *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*
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.

Other Information

Cross-resistance: Amoxicillin on its own shows cross-resistance to other beta-lactams, beta-lactam/beta-lactamase inhibitor combinations, and cephalosporins.

Resistance Mechanisms: Clavulanate protects against resistance mediated by certain beta-lactamase enzymes. The sustained-release formulation of *AUGMENTIN SR* improves efficacy against organisms with resistance mediated by modified penicillin-binding proteins (PBPs).

Pharmacokinetics

a. Absorption:
The two components of *AUGMENTIN* SR (amoxicillin and clavulanate) 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* SR is optimised when taken at the start of a meal.

b. Pharmacokinetics
The pharmacokinetic results that have been obtained for amoxicillin and clavulanate

following the administration of *AUGMENTIN SR* 2 x 1000/62.5 mg to healthy adults at the start of a meal are presented below:

Mean Pharmacokinetic Parameters

Drug administration	**Dose (mg)**	**T>MIC # hours (%)**	**Cmax (mg/l)**	**Tmax (hours)**	**AUC (ug.h/ml)**	**T1/2 (hours)**
		Amoxicillin				
AUGMENTIN SR 1000/62.5mg x 2	2000	5.9 (49.4)	17.0	1.50	71.6	1.27
		Clavulanate				
AUGMENTIN SR 1000/62.5mg x 2	125	ND*	2.05	1.03	5.29	1.03

*ND – Not determinedT>MIC – time above minimum inhibitory concentration

for a MIC of 4 mg/l

The *AUGMENTIN SR* sustained release formulation has a unique pharmacokinetics/pharmacodynamics (PK/PD) profile. The T>MIC obtained with *AUGMENTIN SR* can not be achieved with the same dose formulated as an immediate release tablet.

c. Distribution:
Following intravenous administration of amoxicillin/clavulanate, therapeutic concentrations of both amoxicillin and clavulanate 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 clavulanate is highly protein-bound, studies show that about 25% for clavulanate 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.

d. 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.

Previous studies have shown that, on average, up to approximately 60-70% of the amoxicillin and approximately up to 40-65% of the clavulanate are excreted unchanged in the urine.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanate 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, and as carbon dioxide in expired air.

Pre-clinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core: microcrystalline cellulose PhEUR/NF, sodium starch glycollate BP/NF, colloidal silicon dioxide NF, magnesium stearate PhEUR/NF, xanthan gum NF, citric acid NF.

Film coat (opadry YS 1 7700): hydroxypropylmethylcellulose 2910 6cp PhEUR/USP, hydroxypropylmethylcellulose 2910 15cp PhEUR/USP, titanium dioxide PhEUR/USP, polyethylene glycol 3350 USNF, polyethylene glycol 8000 USNF.

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

AUGMENTIN SR oral presentations should be stored in a dry place at 25°C or below.

Nature and Contents of Container

AUGMENTIN SR tablets: PVC/aluminium or aluminium/aluminium blister strips with one or two film-coated tablets per blister.

Instructions for Use/Handling

No further information of relevance.

Not all presentations are available in every market.

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