AUGMENTIN® BD TABLETS

Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 625 mg tablets: Each tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

AUGMENTIN 1 g tablets: Each tablet contains 875 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

PHARMACEUTICAL FORM

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

AUGMENTIN 1 g tablets: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side.

CLINICAL PARTICULARS

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 β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

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

AUGMENTIN oral presentations for twice daily dosing, are indicated for short-term treatment of bacterial infections at the following sites:

Upper respiratory tract infections (including ENT) e.g. 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.

Dental infections e.g. dentoalveolar abscess

Other infections e.g. septic abortion, puerperal sepsis, 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.

Dosage and Administration

Usual dosages for the treatment of infection

Adults and children over 12 years[+]

Mild - Moderate infections	One *AUGMENTIN* 625 mg tablet twice daily
Severe infections	One *AUGMENTIN* 1 g tablet twice daily

Therapy can be started parenterally and continued with an oral preparation.

Dosage in dental infections (e.g. dentoalveolar abscess)

Adults and children over 12 years[+]: One *AUGMENTIN* 625 mg tablet 2 times a day for five days

[+] *AUGMENTIN* 625 mg and 1 g tablets are not recommended in children of 12 years and under

Dosage in renal impairment

Adults:

The *AUGMENTIN* 1g tablet should only be used in patients with a glomerular filtration rate of >30 ml/min.

Mild impairment (Creatinine clearance >30 ml/min)	Moderate impairment (Creatinine clearance 10-30 ml/min)	Severe impairment (Creatinine clearance <10 ml/min)
No change in dosage (i.e. *either* one 625 mg tablet twice daily *or* one 1 g tablet twice daily)	One 625 mg tablet twice daily. The 1 g tablet should not be administered.	Not more than one 625 mg tablet every 24 hours.

Dosage in hepatic impairment

Dose with caution; monitor hepatic function at regular intervals.

Administration

Tablets should be swallowed whole without chewing. If required, tablets may be broken in half and swallowed without chewing.

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.

AUGMENTIN is also available as *AUGMENTIN* intravenous for the short-term treatment of bacterial infections and for prophylaxis against infection which may be associated with major surgical procedures. *AUGMENTIN* intravenous is described in a separate Pack Insert.

AUGMENTIN is also available as a suspension for three times daily dosing for administration to children under the age of 12 years for the treatment of bacterial infections. *AUGMENTIN* suspension three times daily is described in a separate Pack Insert.

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 (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 *Contra-indications*).

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. *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).*

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

Pregnancy Category B: 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	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.

Not known Aseptic meningitis

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 *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

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*)

To report any side effect(s):

Kingdom of Saudi Arabia
-National Pharmacovigilance centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2353-2354-2334-2340
- Toll-free: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

-GlaxoSmithKline - Head Office, Jeddah

- Tel: 00966(012)6536666
- Fax: 00966(012)6536660
- P.O Box 55850, Jeddah 21544, Saudi Arabia.

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

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 β-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
Gram-positive aerobes:
Bacillius anthracis
Enterococcus faecalis
Listeria monocytogenes
Nocardia asteroides
*Streptococcus pyogenes**†
*Streptococcus agalactiae**†
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
*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.

Pre-clinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

AUGMENTIN 625 mg and 1 g tablets contain the following inactive ingredients: colloidal silicon dioxide, sodium starch glycolate, magnesium stearate (E572), microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol, dimethicone (silicon oil).

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

AUGMENTIN tablets should be stored in un-opened, original packs in a dry place at below 25°C.

Not all presentations are available in every country.

Version number: GDS21/IPI09

Date of issue: 18 January 2013

Manufactured by: SmithKline Beecham plc.* Worthing, UK
Packed by: Glaxo Saudi Arabia Ltd.*, Jeddah, KSA
Marketing Authorisation Holder
Glaxo Saudi Arabia Ltd.* Jeddah, KSA
Address: P.O. Box 22617 Jeddah 21416 – Kingdom of Saudi Arabia
*member of GlaxoSmithKline group of companies

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The Doctor and the Pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

Council of Arab Health Ministers
Union of Arab Pharmacists

AUGMENTIN® SUSPENSION

228 MG/5 ml and 457 MG/5 ml – Mixed fruit flavour

Amoxicillin trihydrate – Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN suspension 228 mg/5 ml contains 200 mg amoxicillin (as amoxicillin trihydrate) and 28.5 mg clavulanic acid (as potassium clavulanate) per 5 ml.

AUGMENTIN suspension 457 mg/5 ml contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate) per 5 ml.

PHARMACEUTICAL FORM

Dry powder for reconstitution in water, at time of dispensing, to form an oral sugar free suspension.

CLINICAL PARTICULARS

Indications

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

AUGMENTIN suspension (228 mg/5 ml and 457mg/5 ml), for twice daily oral dosing, is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Urinary tract infections e.g. cystitis, urethritis, pyelonephritis

Skin and soft tissue infections e.g. cellulitis, animal bites.

Dental infections e.g. severe dental abscess with spreading cellulitis.

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.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with *AUGMENTIN* susceptible beta-lactamase-producing organisms may be treated with *AUGMENTIN* suspension 228 mg/5ml and 457 mg/5 ml. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

Dosage and Administration

The usual recommended daily dosage is:

- 25/3.6 mg/kg/day in mild to moderate infections (upper respiratory tract infections e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections)

- 45/6.4 mg/kg/day for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections)

The tables below give guidance for children.

Children over 2 years

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	5.0 ml *AUGMENTIN* suspension 228 mg/5 ml twice daily ***or*** 2.5 ml *AUGMENTIN* suspension 457 mg/5 ml twice daily.
	7 - 12 years (22 - 40 kg)	10.0 ml *AUGMENTIN* suspension 228 mg/ 5 ml twice daily ***or*** 5.0 ml *AUGMENTIN* suspension 457 mg/5 ml twice daily
45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	10.0 ml *AUGMENTIN* suspension 228 mg/5 ml twice daily ***or*** 5.0 ml *AUGMENTIN* suspension 457 mg/5 ml twice daily
	7 - 12 years	10.0 ml *AUGMENTIN* suspension 457 mg/5 ml twice daily.

Children aged 2 months to 2 years

Children under 2 years should be dosed according to body weight.

AUGMENTIN suspension **457 mg/5 ml**

Weight (kg)	**25/3.6 mg/kg/day** **(**ml / twice daily ***)**	**45/6.4 mg/kg/day** **(**ml / twice daily ***)**
2	0.3	0.6
3	0.5	0.8
4	0.6	1.1
5	0.8	1.4
6	0.9	1.7
7	1.1	2.0
8	1.3	2.3
9	1.4	2.5
10	1.6	2.8
11	1.7	3.1
12	1.9	3.4
13	2.0	3.7
14	2.2	3.9
15	2.3	4.2

*The *AUGMENTIN* suspension 457 mg/5 ml 35 ml and 70 ml presentations may be supplied with a dosing device - See Nature and contents of the container.

There is insufficient experience with *AUGMENTIN* suspension 228 mg/5 ml and 457 mg/5 ml to make dosage recommendations for children under 2 months old.

Renal Impairment

For children with a GFR of >30 ml/min no adjustment in dosage is required. For children with a GFR of <30 ml/min *AUGMENTIN* suspension 228 mg/5 ml and 457 mg/5 ml are not recommended.

Infants with immature kidney function

For infants with immature renal function *AUGMENTIN* suspension 228 mg/5 ml and 457 mg/5 ml are not recommended.

Hepatic Impairment
Dose with caution; monitor hepatic function at regular intervals. There is, as yet, insufficient evidence on which to base a dosage recommendation.

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. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

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 (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*).

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* suspension 228 mg/5 ml and 457 mg/5 ml are not recommended.

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 228 mg/5 ml and 457 mg/5ml suspensions contain 12.5 mg aspartame per 5 ml dose and therefore care should be taken 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 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

Pregnancy Category B: 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	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.
Not known	Aseptic meningitis

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 *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)*

To report any side effect(s):

Kingdom of Saudi Arabia
-National Pharmacovigilance centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2353-2354-2334-2340
- Toll-free: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

-GlaxoSmithKline - Head Office, Jeddah

- Tel: 00966(012)6536666
- Mobile: +966-56-904-9882
- Email: sa.aermi-saudi@gsk.com
- Website: https://healthksa.gsk.com/
- P.O. Box 55850, Jeddah 21544, Kingdom of Saudi Arabia

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

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in *AUGMENTIN* suspension 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 *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
Gram-positive aerobes: *Bacillius anthracis* *Enterococcus faecalis* *Listeria monocytogenes* *Nocardia asteroides* *Streptococcus pyogenes**† *Streptococcus agalactiae**† *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* *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.

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 β-lactamase producing organisms may therefore be treated with *AUGMENTIN*.

Pharmacokinetics

Absorption:

The two components of *AUGMENTIN* suspension 228 mg/5 ml and 457 mg/5 ml, amoxicillin and clavulanate, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of *AUGMENTIN* is optimised when taken at the start of a meal.

The mean AUC values for amoxicillin are essentially the same following twice a day dosing with the *AUGMENTIN* 875/125 mg tablet or three times a day dosing with the *AUGMENTIN* 500/125 mg tablet, in adults. No differences between the 875 mg twice daily and 500 mg three times daily dosing regimes are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

The time of dosing of *AUGMENTIN* relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the *AUGMENTIN* 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_{max}, the highest mean values and smallest inter-subject variabilities were achieved by administering *AUGMENTIN* at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T1/2 and AUC values for amoxicillin and clavulanate are given below for an 875 mg/125 mg dose of amoxicillin /clavulanic acid administered at the start of a meal.

Mean Pharmacokinetic Parameters

Drug Administration	Dose (mg)	Cmax (mg/L)	Tmax* (hours)	AUC (mg.h/L)	T1/2 (hours)
AUGMENTIN 1g					
Amoxicillin	875 mg	12.4	1.5	29.9	1.36
Clavulanate	125 mg	3.3	1.3	6.88	0.92

*Median values

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

Distribution:
The pharmacokinetics of the two components of *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 *AUGMENTIN* approximately doubles the serum levels achieved.

Pre-clinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

Xanthan gum, hydroxypropylmethylcellulose, colloidal silica, succinic acid, silicon dioxide, raspberry, orange “1”, orange “2”, golden syrup dry flavours, aspartame.

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

The dry powder should be stored in unopened containers in a dry place at below 25°C. Reconstituted suspensions should be stored in a refrigerator (2-8°C) and used within seven days.

Nature and Contents of Container

Clear, glass bottles with aluminium screw caps, containing an off-white dry powder. The *AUGMENTIN* suspension 457 mg/5 ml 35 ml and 70 ml presentations may be supplied with a dosing device.
or
Single-dose sachets (*AUGMENTIN* suspension 457 mg/5 ml only).

When reconstituted, an off-white suspension is formed.

Instructions for Use/Handling

GLASS BOTTLES:

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.
- Add volume of water (indicated below). Invert and shake well
- Alternatively, 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.
- Allow to stand for 5 minutes to ensure full dispersion.
- Shake well before taking each dose.

AUGMENTIN suspension 228 mg/5 ml

Fill Weight	**Volume of water to be added to reconstitute**	**Final volume of reconstituted oral suspension**
7.7 g	64 ml	70 ml

15.4 g	128 ml	140 ml

AUGMENTIN suspension 457 mg/5 ml

Fill Weight	**Volume of water to be added to reconstitute**	**Final volume of reconstituted oral suspension**
6.3 g	31 ml	35 ml
12.6 g	62 ml	70 ml
25.2 g	124 ml	140 ml

The *AUGMENTIN* suspension 457 mg/5 ml 35 ml and 70 ml presentation may be provided with a dosing device.

SACHETS:
Single-dose sachets contain powder for a 2.5 ml dose of *AUGMENTIN* suspension 457 mg/5 ml.

Directions for use: Check that the sachet is intact before use

1. Cut sachet along dotted line. Empty contents into a glass
2. Half fill sachet with water
3 Pour into a glass, stir to mix
4. Drink immediately upon reconstitution

If two or four sachets have to be taken at once then they can be mixed in the same glass.

Not all presentations are available in every country.

INSTRUCTIONS TO THE PATIENT

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

- Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are experts in medicine, its benefits and risks.

- Do not by yourself, interrupt the period of treatment prescribed for you.

- Do not repeat the same prescription without consulting your doctor.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN

Council of Arab Health Ministers

Union of Arab Pharmacists

Manufactured by:

Glaxo Wellcome Production*, Mayenne, France

Packed by:

Glaxo Saudi Arabia Ltd.*, Jeddah, KSA

MAH:

Glaxo Saudi Arabia Ltd.*, Jeddah, KSA

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