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AUGMENTIN™ INTRAVENOUS

Amoxicillin sodium - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 600 mg intravenous: 500 mg amoxicillin (as amoxicillin sodium) and 100 mg clavulanic acid (as potassium clavulanate) for reconstitution as an intravenous injection or infusion.
AUGMENTIN 1.2 g intravenous: 1 g amoxicillin (as amoxicillin sodium) and 200 mg clavulanic acid (as potassium clavulanate) for reconstitution as an intravenous injection or infusion.

PHARMACEUTICAL FORM

Sterile powder for injection.

CLINICAL PARTICULARS

Indications

AUGMENTIN should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.
AUGMENTIN is 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 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.
Other infections e.g. intra-abdominal sepsis.
AUGMENTIN intravenous is also indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastrointestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract.
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 β-lactamase producing organisms may therefore be treated with *AUGMENTIN*.

Dosage and Administration

Dosage for the treatment of infections

Adults and children over 12 years:	Usually 1.2 g eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 3 months-12 years:	Usually 30 mg/kg * *AUGMENTIN* eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 0-3 months:	30 mg/kg* *AUGMENTIN* every 12 hours in premature infants and in full term infants during the perinatal period, increasing to eight hours thereafter. * Each 30 mg *AUGMENTIN* contains 25 mg amoxicillin and 5 mg clavulanate.

Adult dosage for surgical prophylaxis
The usual dose is 1.2 g *AUGMENTIN* intravenous given at the induction of anaesthesia. Operations where there is a high risk of infection, e.g. colorectal surgery, may require three, and up to four, doses of 1.2 g *AUGMENTIN* intravenous in a 24-hour period. These doses are usually given at 0, 8, 16 (and 24) hours. This regimen can be continued for several days if the procedure has a significantly increased risk of infection.
Clear clinical signs of infection at operation will require a normal course of intravenous or oral *AUGMENTIN* therapy post-operatively.

Dosage in renal impairment
Adults

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	1.2 g IV stat., followed by 600 mg IV 12 hourly	1.2 g IV stat., followed by 600 mg IV 24 hourly. Dialysis decreases serum concentrations of *AUGMENTIN* and an additional 600 mg IV dose may need to be given during dialysis and at the end of dialysis

Children
Similar reductions in dosage should be made for children.

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.
Each 1.2 g vial of *AUGMENTIN* contains 1.0 mmol of potassium and 3.1 mmol of sodium (approx.).

Administration
AUGMENTIN intravenous may be administered either by intravenous injection or by intermittent infusion. *It is not suitable for intramuscular administration.*

Contraindications

AUGMENTIN is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins
AUGMENTIN is contraindicated 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, 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*).
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.
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.
If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.
In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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*).
The presence of clavulanic acid in *AUGMENTIN* may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

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

Use in Pregnancy
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 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, especially during the first trimester, unless considered essential by the physician.

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

Vascular disorders
Rare — Thrombophlebitis at the site of injection

Gastrointestinal disorders
Common — Diarrhoea
Uncommon — Nausea, vomiting, indigestion
Very rare — Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis – *see Warnings and Precautions)* are less likely to occur after parenteral administration.

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)
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 can be removed from the circulation by haemodialysis.
Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

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 ß-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
Gardnerella vaginalis
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 faeciium

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. 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
None.

Incompatibilities
AUGMENTIN intravenous should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If *AUGMENTIN* is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
AUGMENTIN vials should be stored in a dry place below 25°C.

Nature and Contents of Container
Glass vials (Ph.Eur. type I) fitted with butyl rubber bungs and aluminium overseals containing sterile white powder.

Instructions for Use/Handling
600 mg vial: To reconstitute dissolve in 10 ml Water for Injections BP. (Final volume 10.5 ml)
1.2 g vial: To reconstitute dissolve in 20 ml Water for Injections BP. (Final volume 20.9 ml)
A transient pink coloration may or may not appear during reconstitution. Reconstituted solutions are normally colourless or a pale, straw colour.
Intravenous injection:
The stability of *AUGMENTIN* intravenous solution is concentration dependent, thus *AUGMENTIN* intravenous should be used immediately upon reconstitution and given by slow intravenous injection over a period of 3-4 minutes. *AUGMENTIN* intravenous solutions should be used within 20 minutes of reconstitution. *AUGMENTIN* may be injected directly into a vein or via a drip tube.
Intravenous infusion:
Alternatively, *AUGMENTIN* intravenous may be infused in Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v). Add, without delay*, 600 mg reconstituted solution to 50 ml infusion fluid or 1.2 g reconstituted solution to 100 ml infusion fluid (e.g. using a minibag or in-line burette). Infuse over 30-40 minutes and complete within four hours of reconstitution. For other appropriate infusion fluids, see *Stability and Compatibility* section.
*Solutions should be made up to full infusion volume immediately after reconstitution.
Any residual antibiotic solutions should be discarded.
Therapy can be started parenterally and continued with an oral preparation.
Treatment should not be extended beyond 14 days without review.

Stability and Compatibility
Intravenous infusions of *AUGMENTIN* may be given in a range of different intravenous fluids. Satisfactory antibiotic concentrations are retained at 5°C and at room temperature (25°C) in the recommended volume of the following infusion fluids. If reconstituted and maintained at room temperature, infusions should be completed within the times stated.

Intravenous infusion fluids	Stability period at 25°C
Water for Injections B.P.	4 hours
Sodium Chloride Intravenous Infusion B.P. (0.9% w/v)	4 hours
Sodium Lactate Intravenous Infusion B.P. (one-sixth molar)	4 hours
Compound Sodium Chloride Intravenous Infusion B.P. (Ringer's Solution)	3 hours
Compound Sodium Lactate Intravenous Infusion B.P. (Ringer-Lactate Solution; Hartmann's Solution)	3 hours
Potassium Chloride and Sodium Chloride Intravenous Infusion B.P.	3 hours

Reconstituted solutions should not be frozen.
AUGMENTIN is less stable in infusions containing glucose, dextran or bicarbonate.
Reconstituted solutions of *AUGMENTIN* should therefore not be added to such infusions but may be injected into the drip tubing over a period of 3-4 minutes.
For storage at 5°C, the reconstituted solution should be added to pre-refrigerated infusion bags which can be stored for up to 8 hours. Thereafter, the infusion should be administered immediately after reaching room temperature.

Intravenous infusion fluids	Stability period at 5°C
Water for Injections B.P.	8 hours
Sodium Chloride Intravenous Infusion B.P. (0.9% w/v)	8 hours

Not all presentations are available in every country.

Manufactured by:
SmithKline Beecham plc*
Worthing
UK
*Member of the GlaxoSmithKline group of companies

Version number: GDS28/IPI09
Date of issue: 18 January 2013

GlaxoSmithKline

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