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Version: 2 gsk

Harmony AMS
Artwork Information Panel

Manufacturing Site Number:
62000000052147

Manufacturing Site(s):
GSK_WORTHING_UNITED KINGDOM

Product Market Trade Name:
Augmentin

Approving Market(s):
CFUN-GRA Labelling-General Export Pack

Print Process:
N/A

Colour Standard Reference:
N/A

Technical Drawing (Do NOT include version number):
LF035

Material Spec. (Do NOT include version number):
N/A

Material Type:
N/A | N/A

Total Colours & Varnishes: 2

BLACK		527	

Total Special Finishes: 0

Body Text Size:
8.0pt

Smallest Text Size:
8.0pt

Leading:
9.0pt

Horizontal Scale:
95%

Microtext:
N

Additional Info (1):
N/A

Additional Info (2):
N/A

Additional Info (3):
N/A

200 mm Measuring Bar

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NOTE TO MARKET

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IMPORTANT

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Shelf Life

PHARMA CODE N° 3601

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

Dosage depends on the age and renal function of the patient and the severity of the infection.
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.
Tablets should be swallowed whole without chewing. If required, tablets may be broken in half and swallowed without chewing.
AUGMENTIN tablets are not recommended in children of 12 years and under.

Adults and Children over 12 years

The usual recommended daily dosage is:

Mild - Moderate infections	One *AUGMENTIN* 625 mg tablet every 12 hours.
Severe infections	One *AUGMENTIN* 1 g tablet every 12 hours.

Renal Impairment

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min. The *AUGMENTIN* 1g tablet should only be used in patients with a creatinine clearance (CrCl) rate of more than 30 mL/min.

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

Hepatic Impairment

Dose with caution; monitor hepatic function at regular intervals.

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 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* 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 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

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 to < 1/10
uncommon ≥ 1/1000 to < 1/100
rare ≥ 1/10,000 to < 1/1000
very rare < 1/10,000.

Infections and infestations

Common — Mucocutaneous candidiasis

Blood and lymphatic system disorders

Rare — Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare — Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare — Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders

Uncommon — Dizziness, headache
Very rare — Reversible hyperactivity, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

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

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Manufacturing Site(s): GSK_WORTHING_UNITED KINGDOM	
Product Market Trade Name: Augmentin	
Approving Market(s): CFUN-GRA Labelling-General Export Pack	
Print Process: N/A	
Colour Standard Reference: N/A	
Technical Drawing (Do NOT include version number): LF035	
Material Spec. (Do NOT include version number): N/A	
Material Type: N/A	N/A
Total Colours & Varnishes: 2	
BLACK	527
Total Special Finishes: 0	
Body Text Size: 8.0pt	
Smallest Text Size: 8.0pt	
Leading: 9.0pt	
Horizontal Scale: 95%	
Microtext: N	
Additional Info (1): N/A	
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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), and drug reaction with eosinophilia and systemic symptoms (DRESS)

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

Renal and urinary disorders

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

Overdose

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

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

AUGMENTIN 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 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
Gram-positive aerobes: *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)
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 tablets contain sodium starch glycolate, magnesium stearate (E572), colloidal silica, microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol, dimeticone (silicone oil).

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not take after the expiry date shown on the pack.
Store in a dry place in the original packaging to protect from moisture.
Refer to pack for storage temperature.
For *AUGMENTIN* tablet packs with a storage temperature up to 25°C, use tablets within 30 days of opening (see also *Instructions for Use/Handling*).
For *AUGMENTIN* tablet packs with a storage temperature up to 30°C, use tablets within 14 days of opening (see also *Instructions for Use/Handling*).
AUGMENTIN tablet packs contain desiccant sachets. Do not remove or eat.

Nature and Contents of Container

AUGMENTIN tablets are suppled in a carton containing blister packs. Each blister pack is stored within a sealed pouch, with a desiccant sachet.

Instructions for Use/Handling

Blister pouches contain a desiccant sachet; do not remove or eat. Discard any opened and unused tablets after storing as directed in the *Special Precautions for Storage* section.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Not all presentations are available in every country.

Manufactured by:
SmithKline Beecham Limited*
Clarendon Road
Worthing
West Sussex, BN14 8QH
United Kingdom.
*Member of GSK group of companies

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