For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

AUGMENTIN 625 / 1g DUO

1. GENERIC NAME

Amoxycillin and Potassium Clavulanate Tablets IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGMENTIN 625 DUO
Each film-coated tablet contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin 500 mg
Potassium Clavulanate Diluted IP equivalent to Clavulanic Acid 125 mg
Colour: Titanium Dioxide IP

List of Excipients
Magnesium stearate, colloidal anhydrous silica, sodium starch glycollate, microcrystalline cellulose, Opaspray KI-7000/Titanium Dioxide suspension, ethylcellulose, propylene glycol, hydroxypropyl methyl cellulose, methylene chloride, methanol and activated dimethicone.

AUGMENTIN 1g DUO
Each film coated tablet contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin 875 mg
Potassium Clavulanate Diluted IP equivalent to Clavulanic Acid 125 mg
Colour: Titanium Dioxide IP

List of Excipients
Magnesium stearate, colloidal silicon dioxide, sodium starch glycollate, microcrystalline cellulose, Opaspray KI-7000/Titanium Dioxide suspension, ethylcellulose, propylene glycol, hydroxypropyl methyl cellulose, methylene chloride, methanol and activated dimethicone.

3. DOSAGE FORM AND STRENGTH

Film-coated tablets.

For information on strengths see *2. Qualitative and Quantitative Composition*.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 amoxycillin 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 625 /1g DUO, are indicated for short-term treatment of bacterial infections at the following sites:

Upper Respiratory Tract Infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower Respiratory Tract Infections e.g. acute exacerbation of chronic obstructive pulmonary disease (AECOPD)/acute exacerbation of chronic bronchitis (AECB), lobar and bronchopneumonia

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

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

Bone and joint infections e.g. osteomyelitis

Dental infections e.g. dentoalveolar abscess

Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis

Susceptibility to *AUGMENTIN* will vary with geography and time (see *5. Pharmacological Properties, 5.2 Pharmacodynamic Properties* for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

4.2 Posology and Method of Administration

Dosage depends on the age and renal function of the patient and the severity of the infection.

To minimize potential gastrointestinal intolerance, administer at the start of a meal.

The absorption of *AUGMENTIN* is optimized when taken at the start of a meal.

Tablets to be consumed in whole, not to be broken.

Treatment should not be extended beyond 14 days without review.

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

AUGMENTIN 625 /1g DUO 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 ***OR*** One *AUGMENTIN* 625 mg tablet every 8 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 amoxycillin and clavulanic acid are decreased.)

Hepatic Impairment

Administer with caution; monitor hepatic function at regular intervals.

4.3 Contraindications

AUGMENTIN is contraindicated

- in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.
- in patients with a previous history of *AUGMENTIN*-associated jaundice/hepatic dysfunction.

4.4 Special Warnings and Precautions for Use

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 *4.3 Contraindications*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to *AUGMENTIN* (see *4.8 Undesirable Effects*). Drug-induced enterocolitis syndrome has been reported mainly in children receiving *AUGMENTIN* (see *4.8 Undesirable Effects*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, *AUGMENTIN* therapy 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 amoxycillin.

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

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

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment *AUGMENTIN* dosage should be adjusted as recommended in *4.2 Posology and Method of Administration*.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxycillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxycillin crystalluria *(*see *4.9 Overdose)*.

4.5 Drug Interactions

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin. Concomitant use with *AUGMENTIN* may result in increased and prolonged blood levels of amoxycillin but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxycillin 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 amoxycillin. 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 amoxycillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

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

4.6 Use in Special Populations

Pregnancy
Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered *AUGMENTIN* have shown no teratogenic effects. In a single study in women with 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, unless considered essential by the physician.

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 known detrimental effects for the breast-fed infant.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

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 (see *4.4 Special Warnings and Precautions for Use*), serum sickness-like syndrome, hypersensitivity vasculitis (see also *Skin and subcutaneous tissue disorders*).

Nervous system disorders

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

Cardiac disorders

Very rare	Kounis syndrome (see *4.4 Special Warnings and Precautions for use.*).

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, drug-induced enterocolitis syndrome - See *4.4 Special Warnings and Precautions for use.)*
	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), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also *Immune system disorders*). If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease.

Renal and urinary disorders

Very rare	Interstitial nephritis, crystalluria (see *4.9 Overdose*)

4.9 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.

Amoxycillin crystalluria, in some cases leading to renal failure, has been observed (see *4.4 Special Warnings and Precautions for Use*).

AUGMENTIN can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Amoxycillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. Amoxycillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxycillin alone does not include organisms which produce these enzymes.

Clavulanic acid 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 clavulanic acid in amoxycillin-clavulanate formulations protects amoxycillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxycillin to include many bacteria normally resistant to amoxycillin and other penicillins and cephalosporins. Thus amoxycillin-clavulanate possesses the distinctive properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

5.2 Pharmacodynamic Properties

ATC code: J01CR02.
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

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

Clavulanate by itself has little antibacterial activity; however, in association with amoxycillin 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 amoxycillin, 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.

5.3 Pharmacokinetic Properties

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 amoxycillin have low levels of serum binding; about 70% remains free in the serum.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

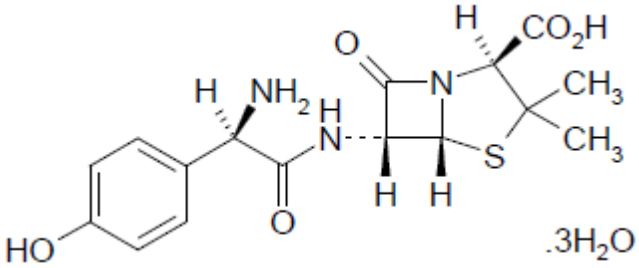
No further information of relevance.

7. DESCRIPTION

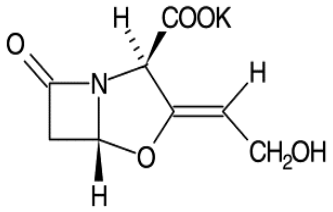
AUGMENTIN (beta-lactam antibacterial penicillin coformulated with a beta-lactamase inhibitor) is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxycillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics.

Chemical Structure
AUGMENTIN is a coformulation of amoxycillin trihydrate and potassium clavulanate.

Amoxycillin trihydrate

Chemical name	(2S,5R,6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
Structural formula	
Molecular formula	$C_{16}H_{19}N_3O_5S \cdot 3H_2O$
Relative molecular mass	365.4 (anhydrous) 419.4 (trihydrate form)

Potassium clavulanate

Chemical name	Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate.
Structural formula	
Molecular formula	$C_8H_8NO_5K$
Relative molecular mass	237.3 (as the potassium salt) 199.2 (as the free acid)

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Aluminium strips.

8.4 Storage and Handling Information

Store protected from moisture at a temperature not exceeding 25°C.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *AUGMENTIN 625 / 1g DUO*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

01-DEC-2023

Version: AUG-TAB/PI/IN/2023/02

Adapted from:
a) *Amoxicillin-clavulanate (Oral) GDS version 29 dated 07 Sep 2023*
b) *Augmentin BD Tablets (Amoxicillin trihydrate - Potassium clavulanate) IPI version 16 dated 07 Sep 2023*
c) *Augmentin TID Tablets and Suspension (Amoxicillin trihydrate - Potassium clavulanate) IPI version 19 dated 07 Sep 2023*