Summary of Product Charecteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Betalac AC 625 Tablets
(Amoxicillin 500mg + Clavulanate 125mg Tablets USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Amoxicillin (As Trihydrate) USP
Equivalent to Amoxicillin 625 mg
Diluted Potassium Clavulanate BP
Equivalent to Clavulanic Acid 125 mg
Excipients q.s

3. PHARMACEUTICAL FORM

Film Coated Tablet for oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amoxicillin-clavulanate is indicated for the treatment of the following bacterial infections when amoxicillin resistant - lactamase-producing strains are suspected as the cause (see section 5.1). In other situations, amoxicillin alone should be considered: Upper respiratory tract infections (including ENT): recurrent tonsillitis, acute sinusitis, acute otitis media; Lower respiratory tract infections: acute exacerbations of chronic bronchitis, community-acquired pneumonia; Urinary tract infections: cystitis (especially when recurrent or complicated – excluding prostatitis), pyelonephritis; Skin and soft tissue infections: cellulitis, animal bites and severe dental abscess with spreading cellulitis; Other infections: septic abortion, puerperal sepsis, intra-abdominal sepsis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Route of administration: oral use Amoxicillin 500mg + Clavulanate 125mg Tablets is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy. Dosage depends on the age, weight and renal function of the patient and the severity of the infection. Dosages are expressed throughout in terms of amoxicillin-/clavulanate content except when doses are stated in terms of an individual component. To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of amoxicillinclavulanate 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 Usual dosage of amoxicillin-clavulanate in adults and adolescents 40 kg is one 500 mg/125 mg tablet taken two times a day. Usual dosages for the treatment of severe infections is one 500/125 mg tablet taken three times a day. More suitable paediatric formulations of amoxicillin-clavulanate are available for the treatment in children.

Elderly No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

Renal impairment In patients with moderate or severe renal impairment, dosages should be adjusted according to the degree of impairment Dosage adjustments are based on the maximum recommended level of amoxicillin

Haemodialysis One 500/125 mg tablet every 24 h, PLUS one 500/125 mg 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. There are insufficient data on which to base a dosage recommendation.

4.3 Contra-indications

Amoxicillin-clavulanate is contraindicated: in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins and to any of the excipients. in patients with a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

4.4 Special Warnings and Special Precautions for Use

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Before initiating therapy with amoxicillin-clavulanate, 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). Change in liver function tests have been observed in some patients receiving Amoxicillin 500mg + Clavulanate 125mg Tablets. The clinical significance of these changes is uncertain but it 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 several weeks after treatment has ceased. In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration– Renal impairment). Amoxicillin 500mg + Clavulanate 125mg Tablets 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. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. 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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin-clavulanate may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid. Prolongation of bleeding time and prothrombin time have been reported in some patients receiving Amoxicillin 500mg + Clavulanate 125mg Tablets. it should be used with care in patients on anti-coagulation therapy. 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 amoxicillin-clavulanate and allopurinol. In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

4.6 Pregnancy and Lactation

This product should only be used in pregnancy or lactation if considered essential by the physician. Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate 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 amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates. Amoxicillin 500mg + Clavulanate 125mg Tablets may be administered during the period of lactation. With the exception of the risk of sensitization, 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

Amoxicillin 500mg + Clavulanate 125mg Tablets has no influence on the ability to drive and use machine

4.8 Undesirable Effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects.

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 (see section 4.4)

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.

Gastrointestinal disorders Very common: Diarrhoea Common: Nausea, vomiting Uncommon: Indigestion Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), black hairy tongue.

Hepatobiliary disorders Uncommon: A moderate rise in AST and/or ALT and alkaline phosphatases 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.

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 section 4.9)

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance. it can be removed from the circulation by haemodialysis. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: -lactam antibacterials, combination of penicillin and beta-lactamase inhibitor ATC code: JOICR02

Mode of action Amoxicillin is a semisynthetic penicillinthat inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall that is usually followed by cell lysis and bacterial death. Clavulanic acid is a beta-lactam agent structurally related to penicillins that can inactivate certain (but not all)

betalactamase enzymes manufactured by bacteria and so can prevent enzymic degradation of amoxicillin. Pharmacokinetic/Pharmacodynamic Relationship The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for beta-lactam agents.. Mechanisms of resistance There are two main mechanisms of resistance to beta-lactam antibiotics, i.e. target (PBP) alteration and inactivation by beta-lactamases. Less often impermeability or efflux pump mechanisms may cause or contribute to bacterial resistance.

5.2 Pharmacokinetic Properties

Absorption The two components, of amoxicillin-clavulanate, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin-clavulanate is optimised when taken at the start of a meal.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (**625** mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA **625** mg/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA **625** mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Distribution Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and

peritoneal fluids, bile and pus. Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ. Co-amoxiclav Bluefish, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant. Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected. Metabolism Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3- carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

Elimination As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 250/125 mg or a single 500/125 mg tablet. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions)

5.3 Preclinical Safety Data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction. Carcinogenicity studies have not been conducted with Augmentin or its components. However, potassium clavulanate alone or combined 1:2 or 1:4 with amoxicillin has been tested in a comprehensive battery of in vitro and in vivo genotoxicity tests which showed no significant genotoxic hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Clellulose
Syliod –FP
Crospovidone
Talc
Clacium Stearate
Insta Moist Shield IC-MS-2398

6.2 Incompatibilities
Not Applicable

6.3 Shelf Life
3 years

6.4 Special Precautions for Storage
Store in a cool, dry place below 30°C. Protect from light

6.5 Nature and Contents of Container
Alu-Alu Packing

6.6 Special precautions for disposal
No special requirements.

Administrative Data

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER
Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
Not Applicable

10. DATE OF (PARTIAL) REVISION OF THE TEXT
MARCH, 2018

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