SUMMARY OF PRODUCT CHARACTERISTICS

AMCLAVIN 312.5

(Amoxicillin and Clavulanate Potassium for Oral Suspension BP 312.5 mg)

1. Name of the medicinal product

AMCLAVIN 312.5

2. Qualitative and quantitative composition

Each 5 ml of the reconstituted suspension contains:

Amoxicillin Trihydrate BP

Eq. to Amoxicillin……250 mg

Diluted Potassium Clavulanate BP

Eq to Clavulanic acid……62.5 mg

Excipients……..q.s

In a Flavoured Syrupy Base

3. Pharmaceutical form

Powder for oral suspension.

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

4. Clinical particulars

4.1 Therapeutic indications

AMCLAVIN 312.5 is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Children < 40 kg

20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

The dose of AMCLAVIN 312.5 that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

Method of administration

Shake to loosen powder, add water as directed, invert and shake.

Shake the bottle before each dose.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-

lactam agent (e.g. a cephalosporin, carbapenem or monobactam), jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4 Special warnings and precautions for use

This product is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant S. pneumoniae.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment and renal impairment.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be taken while administering Amoxicillin/Clavulanic acid concomitantly with oral anticoagulants, methotrexate, probenecid and mycophenolate mofetil.

It may lead to increased prothrombin time, increased cases of toxicity and decrease the renal tubular secretion of amoxicillin.

4.6 Pregnancy and Lactation

Pregnancy: Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactation: Both substances are excreted into breast milk. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur such as allergic reactions, dizziness, convulsions, which may influence the ability to drive and use machines.

4.8 Undesirable effects

The commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting also.

Very rarely side effects such as overgrowth of non-susceptible organisms, reversible leucopenia (including neutropenia), thrombocytopenia, reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time, immune system disorders, angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis, nervous system disorders, dizziness, headache, reversible hyperactivity, convulsions, aeseptic meningitis, diarrhoea, antibiotic-associated colitis, black hairy tongue, tooth discolouration, rises in AST and/or ALT5, hepatitis, cholestatic jaundice, skin rash, pruritus, urticarial, erythema multiforme, stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), interstitial nephritis and crystalluria may be observed.

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mode of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that 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, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (μg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤1	-	>1
Moraxella catarrhalis[1]	≤1	-	>1
Staphylococcus aureus[2]	≤2	-	>2
Coagulase-negative staphylococci[2]	≤0.25		>0.25
Enterococcus[1]	≤4	8	>8
Streptococcus A, B, C, G[5]	≤0.25	-	>0.25
Streptococcus pneumoniae[3]	≤0.5	1-2	>2
Enterobacteriaceae[1,4]	-	-	>8
Gram-negative Anaerobes[1]	≤4	8	>8

Gram-positive Anaerobes[1]	≤4	8	>8
Non-species related breakpoints[1]	≤2	4-8	>8

[1]The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.

[2]The reported values are Oxacillin concentrations.

[3]Breakpoint values in the table are based on Ampicillin breakpoints.

[4]The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.

[5]Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive micro-organisms: Enterococcus faecalis, Gardnerella vaginalis, Staphylococcus aureus (methicillin-susceptible)[£], Coagulase-negative staphylococci (methicillin-susceptible), Streptococcus agalactiae, Streptococcus pneumoniae[1], Streptococcus pyogenes and other beta-haemolytic streptococci and Streptococcus viridans group.

Aerobic Gram-negative micro-organisms: Capnocytophaga spp., Eikenella corrodens, Haemophilus influenzae[2], Moraxella catarrhalis and Pasteurella multocida

Anaerobic micro-organisms: Bacteroides fragilis, Fusobacterium nucleatum and Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms: Enterococcus faecium[$]

Aerobic Gram-negative micro-organisms: Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Proteus mirabilis and Proteus vulgaris

Inherently resistant organisms

Aerobic Gram-negative micro-organisms: Acinetobacter sp., Citrobacter freundii, Enterobacter sp., Legionella pneumophila, Morganella morganii, Providencia spp., Pseudomonas sp., Serratia sp. and Stenotrophomonas maltophilia

Other micro-organisms: Chlamydophila pneumonia, Chlamydophila psittaci, Coxiella burnetti and Mycoplasma pneumonia

[$]Natural intermediate susceptibility in the absence of acquired mechanism of resistance. [£]All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]Streptococcus pneumoniae that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid.

[2]Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption: 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/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose	C_{max}	T_{max}*	$AUC_{(0-24h)}$	T ½
	(mg)	(µg/ml)	(h)	(µg.h/ml)	(h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 9.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid *Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution: About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation: Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination: The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. 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 single AMCLAVIN 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue. Carcinogenicity studies have not been conducted with AMCLAVIN or its components.

6. Pharmaceutical particulars

6.1 List of excipients

Colloidal Silicon Dioxide, Methocel-E5 Premium, Aspartame, Succinic acid, Xanthan gum, Rasberry DC 107, Orange dry powder, Pineapple dry powder.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Dry powder: Store in a dry place, below 30ºC.

After reconstitution: Store in a refrigerator (2ºC - 8ºC). Do not freeze.

Once made up, the suspension should be used within 7 days.

6.5 Nature and contents of container

6.6 Powder filled in 100mL glass bottle and glass bottle packed in a carton along with package insert.

6.7 Special precautions for disposal and other handling

Shake bottle to loosen powder.

Add volume of water, 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 exactly to the mark, invert and again shake well.

7. Marketing authorisation holder

Bliss GVS Pharma Ltd.

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