



**National Agency for Food & Drug Administration & Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R) Directorate**

**SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**

Confidential

**DRUG PRODUCT**  
**AMOXICILLIN 500 mg & CLAVULANIC ACID 125 mg TABLETS USP**

**MODULE 1**

**1.4 PRODUCT INFORMATION**

*1.3.1 Summary of Product Characteristics (SPC)*

**1. Name of the medical product**

Drug Product : **MEDICLAV**

Generic Name : Amoxicillin 500 mg & Clavulanic acid 125 mg  
Tablets USP

Strength : Each film coated tablets contains  
Amoxicillin Trihydrate USP equivalent to 500  
mg of Amoxicillin, and Diluted Potassium  
Clavulanate BP equivalent to 125 mg of  
Clavulanic acid.

**2. Qualitative and Quantitative Formula**

**Composition**

Each film coated tablet contains:

Amoxicillin Trihydrate USP

Eq. to Amoxicillin 500 mg

Diluted Potassium Clavulanate BP

Eq. to Clavulanic acid 125 mg

Excipients qs.

Colour: Titanium Dioxide BP

**Qualitative and Quantitative Formula**

Sr. No	Ingredients	Spec.	Label Claim (mg)	Overages	Qty per tablet (mg)
1.	Amoxicillin Trihydrate* eq. to Amoxicillin	USP	500	1.0%	579.639
2.	Diluted Potassium Clavulanate (Avicel 1:1)** eq. to Clavulanic Acid	BP	125	1.0 %	300.730
3.	Crospovidone	USP	NA	Nil	50.000
4.	Microcrystalline Cellulose pH 112***	USP	NA	Nil	39.968
5.	Silicon Dioxide	USP	NA	Nil	15.000
6.	Colloidal Silicon Dioxide	USP	NA	Nil	10.000
7.	Magensium Stearate	USP	NA	Nil	11.351

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8.	Microcrystalline Cellulose plain	USP	NA	Nil	10.000
9.	Purified Talc	USP	NA	Nil	1.000
10.	Microcrystalline Cellulose pH 112	USP	NA	Nil	12.304
<b>Coating Material</b>					
12.	Hydroxypropyl Methyl Cellulose (ANYCOAT –C AN 6)	USP	NA	Nil	1.328
13.	Hydroxypropyl Methyl Cellulose (ANYCOAT –C AN 15)	USP	NA	Nil	10.000
14.	Ethyl Cellulose (N-20 CPS)	USP	NA	Nil	0.672
15.	Purified Talc	USP	NA	Nil	0.672
16.	Titanium Dioxide	BP	NA	Nil	6.000
17.	Dibutyl Phthalate	USP	NA	Nil	1.328
18.	#Purified Talc	USP	NA	Nil	0.672
19.	#Methylene Dichloride	USP	NA	Nil	306.672
20.	#Isopropyl Alcohol	USP	NA	Nil	93.328

\*Amoxicillin Trihydrate 1.1478 mg is approximately equivalent to 1.0 mg of Amoxicillin.

\*\* Diluted Potassium Clavulanate 2.382 mg is approximately equivalent to 1.0 mg of Clavulanic acid.

The quantity of Amoxicillin Trihydrate to be taken on 100% assay basis inclusive of 1.0% overages. Actual quantity to be used after calculation of assay of Amoxicillin Trihydrate on as such basis.

The quantity of Diluted Potassium Clavulanate to be taken on 100% assay basis inclusive of 1.0% overages. Actual quantity to be used after calculation of assay of Clavulanic acid on as such basis

\*\*\*Actual quantity dispensed of Amoxicillin and Clavulanic acid to be compensated with respect to Microcrystalline Cellulose pH 112

# Does not appears in final product.

**Abbreviations**

USP : United States Pharmacopeia  
BP : British Pharmacopoeia  
qs. : Quantity Sufficient

**3. Pharmaceutical Form**

Film coated tablets for oral use only.

White to off white coloured elongated biconvex film coated tablets, plain on both sides.

**4. Clinical Particulars**

**4.1 Therapeutic Indications**

Amoxicillin and Clavulanate Potassium Tablets is indicated for the treatment of the following infections in adults and children.

- Acute bacterial sinusitis (adequately diagnosed)
- Cystitis
- Pyelonephritis
- Cellulitis
- Animal bites
- Severe dental abscess with spreading cellulitis.

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## **4.2 Posology and Method of administration**

### **Posology**

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Amoxicillin and Clavulanate Potassium Tablets 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.

The use of alternative presentations of Amoxicillin and Clavulanate Potassium Tablets (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

For adults and children  $\geq 40$  kg, this formulation of Amoxicillin and Clavulanate Potassium Tablets provides a total daily dose of 750 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Amoxicillin and Clavulanate Potassium Tablets is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

Treatment should not be extended beyond 14 days without review.

### **Adults and children $\geq 40$ kg**

One tablet taken three times a day.

### **Children $< 40$ kg**

Amoxicillin and Clavulanate Potassium Tablets 250 mg/125 mg film-coated tablets are not recommended in children  $< 40$  kg.

### **Elderly**

No dose adjustment is considered necessary.

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**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.

***Adults and children  $\geq$  40 kg***

CrCl: 10-30 ml/min	250 mg/125 mg twice daily
CrCl < 10 ml/min	250 mg/125 mg once daily
Haemodialysis	Two doses of 250 mg/125 mg every 24 hours, plus two doses of 250 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

***Children < 40 kg***

In children < 40 kg with creatinine clearance less than 30 ml/min, the use of Amoxicillin and Clavulanate Potassium Tablets presentations with an amoxicillin to clavulanic acid ratio of 2:1 is not recommended, as no dose adjustments are available. In such patients, Amoxicillin and Clavulanate Potassium Tablets formulations with an amoxicillin to clavulanic acid ratio of 4:1 are recommended.

**Hepatic impairment**

Dose with caution and monitor hepatic function at regular intervals .

**Method of administration**

Amoxicillin and Clavulanate Potassium Tablets is for oral use.

Amoxicillin and Clavulanate Potassium Tablets should be administered with a meal to minimise potential gastrointestinal intolerance.

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### **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).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid

### **4.4 Special warnings and precautions for use**

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

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 and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of amoxicillin/clavulanic acid 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*.

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

Amoxicillin/clavulanic acid 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.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

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

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The occurrence at the treatment initiation of a feverish generalised erythema associated with pustule may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires Co-amoxiclav discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. 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. In all populations, 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.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Antiperistaltic medicinal products are contraindicated in this situation.

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

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

In patients with renal impairment, the dose should be adjusted according to the degree of impairment

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. In patients with bladder catheters, a regular check of patency should be maintained.

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During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non- enzymatic methods.

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

There have been reports of positive test results using the Bio-Rad Laboratories *Platelia Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### **Oral anticoagulants**

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are 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 amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

##### **Methotrexate**

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

##### **Probenecid**

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



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### **Mycophenolate mofetil**

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. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

## **4.6 Fertility, 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. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

### **Breast-feeding**

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). 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. The possibility of sensitisation should be taken into account.

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 (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

#### 4.8 Undesirable effects

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

The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common ( $\geq 1/10$ ) Common ( $\geq 1/100$  to  $< 1/10$ ) Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

<u>Infections and infestations</u>	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
<u>Blood and lymphatic system disorders</u>	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time <sup>1</sup>	Not known
<u>Immune system disorders</u> <sup>10</sup>	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
<u>Nervous system disorders</u>	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions <sup>2</sup>	Not known
Aseptic meningitis	Not known
<u>Gastrointestinal disorders</u>	
Diarrhoea	Common
Nausea <sup>3</sup>	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis <sup>4</sup>	Not known
Black hairy tongue	Not known
Tooth discolouration <sup>11</sup>	Not known
<u>Hepatobiliary disorders</u>	
Rises in AST and/or ALT <sup>5</sup>	Uncommon
Hepatitis <sup>6</sup>	Not known
Cholestatic jaundice <sup>6</sup>	Not known
<u>Skin and subcutaneous tissue disorders</u> <sup>7</sup>	

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Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP) <sup>9</sup>	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
<u>Renal and urinary disorders</u>	
Interstitial nephritis	Not known
Crystalluria <sup>8</sup>	Not known

#### **4.9 Overdose**

##### **Symptoms and signs of 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. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.

##### **Treatment of intoxication**

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.**

##### **Mechanism 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).

<b>Organism</b>	<b>Susceptibility Breakpoints (<math>\mu\text{g/ml}</math>)</b>		
	<b>Susceptible</b>	<b>Intermediate</b>	<b>Resistant</b>
Haemophilus influenzae1	$\leq 1$	-	$> 1$
Moraxella catarrhalis1	$\leq 1$	-	$> 1$
Staphylococcus aureus2	$\leq 2$	-	$> 2$
Coagulase-negative staphylococci2	$\leq 0.25$		$> 0.25$
Enterococcus1	$\leq 4$	8	$> 8$
Streptococcus A, B, C, G5	$\leq 0.25$	-	$> 0.25$

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Streptococcus pneumoniae <sup>3</sup>	≤ 0.5	1-2	> 2
Enterobacteriaceae <sup>1,4</sup>	-	-	> 8
Gram-negative Anaerobes <sup>1</sup>	≤ 4	8	> 8
Gram-positive Anaerobes <sup>1</sup>	≤ 4	8	> 8
Non-species related breakpoints <sup>1</sup>	≤ 2	4-8	> 8

**Commonly susceptible species Aerobic**
Gram-positive micro-organisms

*Enterococcus faecalis*

*Gardnerella vaginalis*

*Staphylococcus aureus* (methicillin-susceptible)<sup>‡</sup>

Coagulase-negative *staphylococci* (methicillin-susceptible)

*Streptococcus agalactiae*

*Streptococcus pneumoniae*<sup>1</sup>

*Streptococcus pyogenes* and other beta-haemolytic *streptococci*

*Streptococcus viridans* group

Aerobic Gram-negative micro-organisms

*Capnocytophaga* spp.

*Eikenella corrodens*

*Haemophilus influenzae*<sup>2</sup>

*Moraxella catarrhalis*

*Pasteurella multocida*

Anaerobic micro-organisms

*Bacteroides fragilis*

*Fusobacterium nucleatum*

*Prevotella* spp.

**Species for which acquired resistance may be a problem**
Aerobic Gram-positive micro-organisms

*Enterococcus faecium*<sup>§</sup>

Aerobic Gram-negative micro-organisms

*Escherichia coli*

*Klebsiella oxytoca*

*Klebsiella pneumoniae*

*Proteus mirabilis*

*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.

*Stenotrophomonas maltophilia*

Other micro-organisms

*Chlamydophila pneumoniae*

*Chlamydophila psittaci*

*Coxiella burnetti* *Mycoplasma pneumoniae*

<sup>§</sup> Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

<sup>‡</sup>All methicillin-resistant *staphylococci* are resistant to amoxicillin/clavulanic acid  
<sup>1</sup>*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid  
<sup>2</sup> 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. 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 ( $T_{max}$ ) 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 ( $\pm$ SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	$C_{max}$ ( $\mu\text{g/ml}$ )	$T_{max}$ * (h)	AUC <sub>(0-24h)</sub> ( $\mu\text{g.h/ml}$ )	T 1/2 (h)
Amoxicillin					
AMX/CA 500 mg/125 mg	500	7.19 $\pm$ 2.26	1.5 (1.0-2.5)	53.5 $\pm$ 8.87	1.15 $\pm$ 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 $\pm$ 0.83	1.5 (1.0-2.0)	15.72 $\pm$ 3.86	0.98 $\pm$ 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.

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Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

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 amoxicillin/clavulanic acid 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.

**Age**

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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### **Gender**

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

### **Renal impairment**

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid .

### **Hepatic impairment**

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional 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 amoxicillin/clavulanic acid or its components.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Crospovidone  
Microcrystalline Cellulose pH 12  
Silicon Dioxide  
Colloidal Silicon Dioxide  
Magnesium Stearate  
Purified Talc  
Hydroxypropyl Methyl Cellulose  
Ethyl Cellulose  
Titanium Dioxide

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Dibutyl Phthalanate  
Methylene Dichloride  
Isopropyl Alcohol

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

30 months

**6.4 Special precautions for storage**

Do not store above 30°C. Store in the original container

**6.5 Nature and contents of container**

ALU-ALU blister pack of 7 tablets along with patient Information leaflet.

Printed Aluminium Top foil

ALU-ALU Base foil

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. How supplied**

White to off white elongated biconvex film coated tablets, plain on both sides, packed in a ALU-ALU blister pack of 7 tablets.

**Pack Style:. 2 x 7 Tabs**

White to off white coloured elongated biconvex film coated tablets, plain on both sides , packed in a ALU-ALU blister pack of 7 tablets. Such 2 ALU-ALU packs containing 7 tablets each placed in a printed laminated carton along with patient information leaflet

**Confidential**

**DRUG PRODUCT**  
**AMOXICILLIN 500 mg & CLAVULANIC ACID 125 mg TABLETS USP**

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**MODULE 1**

**8. Storage condition**

Do not store above 30°C. Protect from light and moisture.

**9.0 Manufacturer**

**MEDICEF PHARMA**

Plot No. 28,29 & 48 EPIP, Phase 1  
Jharmajri, Baddi, Distt: Solan, (H.P), Republic of INDIA

**10.0 Applicant**

**SK MEDICINES LTD**

3rd FLOOR, TOWER FERNADEZ, 1-9, BERKLEY STREET, ONIKAN,  
LAGOS, NIGERIA

**10.0 Address of Local Technical Representative**

**SK MEDICINES LTD**

3rd FLOOR, TOWER FERNADEZ, 1-9, BERKLEY  
STREET, ONIKAN, LAGOS, NIGERIA