

## Summary of Product Characteristics for Pharmaceutical Products

### 1. Name of the medicinal product:

ACINET DRY SYRUP 642.9 mg/5 ml

### 2. Qualitative and quantitative composition

Each 5 ml of reconstituted suspension Contains:

Amoxicillin trihydrate equivalent to Amoxicillin 600mg

Diluted potassium clavulanate equivalent to clavulanic acid 42.9 mg

Excipients with known effect

Each 5 ml of reconstituted ACINET 642.9 contains:

10.90mg of Sodium benzoate

36.36mg of Aspartame

For a full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Powder for oral suspension

White granular powder filled in 100 ml amber colour glass bottle, on reconstitution gives white colour suspension.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL is indicated for the treatment of paediatric patients with **recurrent or persistent acute otitis media** due to;

- S. pneumoniae,
- H. influenzae including,  $\beta$ -lactamase-producing strains
- M. catarrhalis, including  $\beta$ -lactamase-producing strains

Characterized by the following risk factors:

- Antibiotic exposure for acute otitis media within the preceding 3 Months.
- Either of the following: -age  $\leq$  2 years

#### 4.2 Posology and method of administration

Amoxicillin and Clavulanate Potassium, 600 mg/42.9 mg per 5 mL, does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other suspensions of AMOXICILLIN AND CLAVULANATE POTASSIUM. Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg

per 5 mL contains 42.9 mg of clavulanic acid per 5. Therefore, it should not be substituted for other preparations of Amoxicillin/clavulanic acid.

Dosage:

Paediatric patients 3 months and older: Based on the amoxicillin component (600 mg/5 mL), the recommended dose of Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL is 90 mg/kg/day divided every 12 hours, administered for 10 days (see chart below).

**Elderly**

No dose adjustment is considered necessary. Elderly patients should be treated with adult formulations of Clavace.

**Renal impairment**

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

In patients with creatinine clearance less than 30 ml/min, the use of Clavace 457 mg presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

**Hepatic impairment**

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

**Method of administration**

Clavace 457 mg is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according to the SmPC of the IV formulation and continued with an oral preparation.

**Method of Administration**

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

Shake the bottle before each dose (see section 6.6).

**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	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 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

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.

### Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

### Administration

Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid.

Prepare a suspension at time of dispensing as follows:

1. Tap bottle until all the powder flows freely.
2. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder.
3. Add remainder of the water and again shake vigorously.

<b>Bottle Size (ML)</b>	<b>Amount of water required for reconstitution (ML)</b>
75	70
142	90
200	180

Every 5 ml of reconstituted suspension contains 600 mg of Amoxycillin and 42.9 mg of clavulanic acid.

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).

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 (see sections 4.3 and 4.8).

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

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug use) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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

This presentation of Clavace 457 mg 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.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires Clavace discontinuation and contra-indicates 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. Anti-peristaltic medicinal products are contra-indicated 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.

During treatment with Clavace 457 mg, 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 Clavace 457 mg 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.

Clavace 457 mg suspension contains aspartame, it should be administered with caution in patients with phenylketonuria. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Clavace 457 mg suspension contains sodium benzoate (see section 2 for quantities). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue). Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Clavace 457 mg suspension contains mannitol (see section 2) which may have a mild laxative effect.

#### **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 (see sections 4.4 and 4.8).

##### 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.

##### 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 necrotizing enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

### Lactation

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhea 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 (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

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## **4.8 Undesirable effects**

The most commonly reported adverse drug reactions (ADRs) are

diarrhea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Amoxicillin/clavulanic acid, 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)

<b>Infections and infestations</b>	
<b>Mucocutaneous candidosis</b>	<b>Common</b>
<b>Overgrowth of non-susceptible organisms</b>	<b>Not known</b>
<b>Blood and lymphatic system disorders</b>	
<b>Reversible leucopenia (including neutropenia)</b>	<b>Rare</b>
<b>Thrombocytopenia</b>	<b>Rare</b>
<b>Reversible agranulocytosis</b>	<b>Not known</b>
<b>Haemolytic anaemia</b>	<b>Not known</b>
<b>Prolongation of bleeding time and prothrombin time<sup>1</sup></b>	<b>Not known</b>
<b>Immune system disorders<sup>10</sup></b>	
<b>Angioneurotic oedema</b>	<b>Not known</b>
<b>Anaphylaxis</b>	<b>Not known</b>
<b>Serum sickness-like syndrome</b>	<b>Not known</b>
<b>Hypersensitivity vasculitis</b>	
<b>Not known</b>	<b>Not known</b>
<b>Nervous system disorders</b>	
<b>Dizziness</b>	<b>Uncommon</b>
<b>Headache</b>	<b>Uncommon</b>
<b>Reversible hyperactivity</b>	<b>Not known</b>
<b>Convulsions<sup>2</sup></b>	<b>Not known</b>

<b>Gastrointestinal disorders</b>	
<b>Diarrhoea</b>	<b>Common</b>
<b>Nausea<sup>3</sup></b>	<b>Common</b>
<b>Vomiting</b>	<b>Common</b>
<b>Indigestion</b>	<b>Uncommon</b>
<b>Antibiotic-associated colitis<sup>4</sup></b>	<b>Not known</b>
<b>Black hairy tongue</b>	<b>Not known</b>
<b>Tooth discolouration<sup>11</sup></b>	<b>Not known</b>
<b>Hepatobiliary disorders</b>	
<b>Rises in AST and/or ALT<sup>5</sup></b>	<b>Uncommon</b>
<b>Hepatitis<sup>6</sup></b>	<b>Not known</b>
<b>Cholestatic jaundice<sup>6</sup></b>	<b>Not known</b>
<b>Skin and subcutaneous tissue disorders <sup>7</sup></b>	
<b>Skin rash</b>	<b>Uncommon</b>
<b>Pruritus</b>	<b>Uncommon</b>
<b>Urticaria</b>	<b>Uncommon</b>
<b>Erythema multiforme</b>	<b>Rare</b>
<b>Stevens-Johnson syndrome</b>	<b>Not known</b>
<b>Toxic epidermal necrolysis</b>	<b>Not known</b>
<b>Bullous exfoliative-dermatitis</b>	<b>Not known</b>
<b>Acute generalised exanthemous pustulosis (AGEP)<sup>9</sup></b>	<b>Not known</b>
<b>Renal and urinary disorders</b>	
<b>Interstitial nephritis</b>	<b>Not known</b>
<b>Crystalluria<sup>8</sup></b>	<b>Not known</b>
<sup>1</sup> See section 4.4	
<sup>2</sup> See section 4.4	

<sup>3</sup> Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking Clavace at the start of a meal.

<sup>4</sup> Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)

<sup>5</sup> 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.

<sup>6</sup> These events have been noted with other penicillins and cephalosporins (see section 4.4).

<sup>7</sup> If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

<sup>8</sup> See section 4.9

<sup>9</sup> See section 4.4

<sup>10</sup> See sections 4.3 and 4.4

<sup>11</sup> Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

### Reporting of suspected adverse reactions:

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

## **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.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

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 hemodialysis.

## **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 ( $\mu\text{g} / \text{ml}$ )		
	Susceptible	Intermediate	Resistant
<i>Haemophilus influenzae</i> <sup>1</sup>	1 $\leq$	-	> 1
<i>Moraxella catarrhalis</i> <sup>1</sup>	1 $\leq$	-	> 1
<i>Staphylococcus aureus</i> <sup>2</sup>	2 $\leq$	-	> 2
Coagulase-negative staphylococci <sup>2</sup>	0.25		> 0.25
<i>Enterococcus</i> <sup>1</sup>	4 $\leq$	8	> 8

<i>Streptococcus A, B, C, G</i> <sup>5</sup>	0.25	-	> 0.25
<i>Streptococcus pneumoniae</i> <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

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

<sup>2</sup> The reported values are Oxacillin concentrations.

<sup>3</sup> Breakpoint values in the table are based on Ampicillin breakpoints.

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

<sup>5</sup> 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 <i>Enterococcus faecalis</i> <i>Gardnerella vaginalis</i> <i>Staphylococcus aureus</i> (methicillin-susceptible) Coagulase-negative staphylococci (methicillin-susceptible) <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <sup>1</sup> <i>Streptococcus pyogenes</i> and other beta-haemolytic streptococci <i>Streptococcus viridans</i> group Aerobic Gram-negative micro-organisms <i>Capnocytophaga</i> spp. <i>Eikenella corrodens</i> <i>Haemophilus influenzae</i> <sup>2</sup> <i>Moraxella catarrhalis</i> <i>Pasteurella multocida</i> Anaerobic micro-organisms <i>Bacteroides fragilis</i> <i>Fusobacterium nucleatum</i> <i>Prevotella</i> spp.

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms <i>Enterococcus faecium</i> § Aerobic Gram-negative micro-organisms <i>Escherichia coli</i> <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Proteus vulgaris</i>
Inherently resistant organisms
Aerobic Gram-negative micro-organisms <i>Acinetobacter</i> sp. <i>Citrobacter freundii</i> <i>Enterobacter</i> sp. <i>Legionella pneumophila</i> <i>Morganella morganii</i> <i>Providencia</i> spp. <i>Pseudomonas</i> sp. <i>Serratia</i> sp. <i>Stenotrophomonas maltophilia</i> Other micro-organisms <i>Chlamydophila pneumoniae</i> <i>Chlamydophila psittaci</i> <i>Coxiella burnetii</i> <i>Mycoplasma pneumoniae</i>
§ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid <sup>1</sup> <i>Streptococcus pneumoniae</i> that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). <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. 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 (T<sub>max</sub>) 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	Cmax	Tmax *	AUC (0-24h)	T 1/2
	(mg)	(µ g/ml)	(h)	((µ g.h/ml)	(h)
Amoxicillin					
AMX/CA	500	7.19	1.5	53.5	1.15
500/125 mg		+/- 2.26	(1.0-2.5)	+/- 8.87	+/- 0.20
Clavulanic acid					
AMX/CA	125	2.40	1.5	15.72	0.98
500 mg/125 mg		+/- 0.83	(1.0-2.0)	+/- 3.86	+/-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.

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 (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

#### 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 Co-amoxiclav 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).

#### 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.

#### 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 (see section 4.2).

#### Hepatic impairment

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

### **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 Clavace or its components.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Aspartame  
Xanthan Gum (Transparent)  
Colloidal Anhydrous Silica  
Sodium Benzoate  
Anhydrous Citric Acid  
Butylated hydroxytoluene  
Orange Flavour  
Silicon dioxide (Syloid-IFP)  
Colour Titanium Dioxide.

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

Powder for reconstitution: 24 months

Reconstituted suspensions should be stored at 2°C – 8°C (but not frozen) for up to 7 days.

### **6.4 Special precautions for storage:**

Powder for reconstitution be stored below 30°C. Keep the container tightly closed.

Oral Suspension: Store at 2°C - 8°C. Do not freeze. Keep the container tightly closed.

Keep out of reach of children.

### **6.5 Nature and contents of container**

100 ml amber colour glass bottle with cap.

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

Not applicable

## **7. Marketing authorization holder and manufacturing site addresses**

**Marketing authorization holder:**

GALAXY PHARMACEUTICAL LTD.  
1st Floor, Doctors Park, 3rd Parkland Avenue,  
P.O.BOX 39107 - 00623,  
Nairobi (Kenya).

**8. Marketing authorization number**  
CTD10454

**9. Date of first registration**  
06/10/2023

**10. Date of revision of the text:**  
05/05/2023

