**Enhancin Tablets 375mg, 625mg & 1 g**
(Amoxicillin and Clavulanate Potassium Tablets)

## 1. NAME OF THE MEDICINAL PRODUCT

**ENHANCIN 375 mg**
**ENHANCIN 625 mg**
**Enhancin Tablets 1 g**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**ENHANCIN 375 mg**
Each tablet contains:
Amoxicillin trihydrate Ph.Eur. equivalent to Amoxicillin……...… 250 mg
Potassium clavulanate Ph.Eur. equivalent to Clavulanic Acid.……125 mg

**ENHANCIN 625 mg**
Each tablet contains:
Amoxicillin trihydrate Ph.Eur. equivalent to Amoxicillin……...… 500 mg
Potassium clavulanate Ph.Eur. equivalent to Clavulanic Acid.……125 mg

**Enhancin Tablets 1 g**
Each tablet contains:
Amoxicillin trihydrate Ph.Eur. equivalent to Amoxicillin……...…875 mg
Potassium clavulanate Ph.Eur. + Microcrystalline cellulose (1:1) equivalent to Clavulanic Acid.……125 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications [1, 2]

To reduce the development of drug resistant bacteria and maintain the effectiveness of amoxicillin/clavulanate potassium and other antibacterial drugs, amoxicillin/clavulanate potassium should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

**Enhancin Tablets 1 gm** are a combination of penicillin-class antibacterial and beta-lactamase inhibitor indicated in the treatment of infections due to susceptible isolates of the designated bacteria in the conditions listed below:

***Lower Respiratory Tract Infections***– caused by β-lactamase-producing isolates of *Haemophilus. influenzae* and *Moraxella catarrhalis*.

***Acute Bacterial Otitis Media***– caused by β-lactamase-producing isolates of *H. influenza* and *M. catarrhalis*.

***Sinusitis***– caused by β-lactamase-producing isolates of *H. influenzae* and *M. catarrhalis*.

***Skin and Skin Structure Infections***– caused by β-lactamase-producing isolates of *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* species.

***Urinary Tract Infections***– caused by β-lactamase-producing isolates of *E. coli*, *Klebsiella* species and *Enterobacter* species.

***Bone and Joint Infections,*** in particular osteomyelitis.

**Limitations of Use**

When susceptibility test results show susceptibility to amoxicillin, indicating no beta-lactamase production, amoxicillin/clavulanate potassium should not be used.

## 4.2 Posology and method of administration [1, 2]

**Enhancin Tablets 1 gm** are not suitable for all dosages and therefore, other suitable available strengths and/or dosage forms of amoxicillin/clavulanate potassium should be used in such cases.

**Enhancin Tablets 1 gm** should not be substituted for other amoxicillin + clavulanate potassium formulations and/or strengths because of the different amoxicillin to clavulanic acid ratios. The use of alternative presentations of amoxicillin + clavulanate potassium (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

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.

***Adults***

The usual adult dose is one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) every 12 hours **OR** one 375 mg tablet (Amoxicillin 250 mg + Clavulanate Potassium 125 mg) every 8 hours.

For more severe infections and infections of the respiratory tract, the dose should be one 1 g tablet (Amoxicillin 875 mg + Clavulanate Potassium 125 mg) every 12 hours **OR** one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) every 8 hours.

***Pediatric Patients***

*Patients Weighing 40 kg or More*

The usual dose is one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) every 12 hours **OR** one 375 mg tablet (Amoxicillin 250 mg + Clavulanate Potassium 125 mg) every 8 hours.

For more severe infections and infections of the respiratory tract, the dose should be one 1 g tablet (Amoxicillin 875 mg + Clavulanate Potassium 125 mg) every 12 hours **OR** one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) every 8 hours.

*Patients Weighing Less Than 40 kg*

**Enhancin Tablets 1 gm** may not be suitable for this patient population and therefore, other suitable available strengths and/or dosage forms of amoxicillin/clavulanate potassium should be used in such cases.

However, the general dosage recommendations of amoxicillin/clavulanate potassium based on the amoxicillin component are as given below:

*Neonates and Infants Aged <12 weeks (<3 months)*

The recommended dose of amoxicillin/clavulanate potassium is 30 mg/kg/day divided every 12 hours, based on the amoxicillin component.

*Patients Aged 12 weeks (3 months) and Older*

See dosing regimens provided in table below. The every 12 hour regimen is recommended as it is associated with significantly less diarrhea.

**Table: Dosing in patients aged 12 weeks (3 months) and older**

| INFECTION | DOSING REGIMEN | |
|---|---|---|
| | **Every 12 hours** | **Every 8 hours** |
| Otitis media[a], sinusitis, lower respiratory tract infections, and more severe infections | 45 mg/kg/day every 12 hours | 40 mg/kg/day every 8 hours |
| Less severe infections | 25 mg/kg/day every 12 hours | 20 mg/kg/day every 8 hours |

[a] Duration of therapy studied and recommended for acute otitis media is 10 days.

***Dosage in Renal Impairment***

*Adults and Children ≥ 40 kg*

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Renal impairment patients with a glomerular filtration rate of <30 ml/min should not receive the 1 gram tablet (Amoxicillin 875 mg + Clavulanate Potassium 125 mg). Patients with a glomerular filtration rate of 10 to 30 ml/min should receive one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) or 375 mg formulation (Amoxicillin 250 mg + Clavulanate Potassium 125 mg) every 12 hours, depending on the severity of the infection. Patients with glomerular filtration rate less than 10 ml/min should receive one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) or 375 mg formulation (Amoxicillin 250 mg + Clavulanate Potassium 125 mg) every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive one 625 mg tablet (Amoxicillin 500 mg + Clavulanate Potassium 125 mg) or 375 mg formulation (Amoxicillin 250 mg + Clavulanate Potassium 125 mg) every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

*Children < 40 kg*

CrCl: 10 to 30 ml/min: Amoxicillin/Clavulanate 15 mg/3.75 mg per kg twice daily (maximum 500 mg/125 mg twice daily).

CrCl < 10 ml /min: Amoxicillin/Clavulanate 15 mg/3.75 mg per kg as a single daily dose (maximum 500 mg/125 mg).

Haemodialysis: Amoxicillin/Clavulanate 15 mg/3.75 mg per kg per day once daily. Prior to haemodialysis, 15 mg/3.75 mg per kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

***Dosage in Hepatic Impairment***

Dose with caution and monitor hepatic function at regular intervals.

***Method of Administration***

**Enhancin Tablets 1 gm** are for oral use.

Amoxicillin/clavulanate potassium may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin/clavulanate potassium is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin/clavulanate potassium should be taken at the start of a meal.

**Dosing in special population**

***Pediatric Use***

Use of amoxicillin/clavulanate potassium in pediatric patients is supported by evidence from reported data of amoxicillin/clavulanate potassium in adults with additional data from a reported study of amoxicillin/clavulanate potassium in pediatric patients aged 2 months to 12 years with acute otitis media.

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed; clavulanate elimination is unaltered in this age group. Dosing of amoxicillin/clavulanate potassium should be modified in pediatric patients aged <12 weeks (<3 months).

***Geriatric Use***

No overall differences in safety or effectiveness have been reported in between elderly (≥65 and ≥75 years old) and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. 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.

***Renal Impairment***

Amoxicillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR <30 ml/min).

## 4.3 Contraindications [1, 2]

Amoxicillin/clavulanate potassium is contraindicated in patients with a history of:

- Severe immediate hypersensitivity/serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillins, cephalosporins, carbapenem or monobactam) or in patients with hypersensitivity to active substance or to penicillin or to any of the excipients of the product.

- Cholestatic jaundice/hepatic impairment due to amoxicillin/clavulanate potassium.

## 4.4 Special warnings and precautions for use [1, 2]

**Hypersensitivity Reactions**

Serious and occasionally fatal hypersensitivity reactions (Including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving beta-lactam antibacterials, including amoxicillin/clavulanate potassium. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens / in atopic individuals. Before initiating therapy with amoxicillin/clavulanate potassium, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactam agents or other allergens. If an allergic reaction occurs, amoxicillin/clavulanate potassium should be

discontinued and appropriate therapy instituted.

**Hepatic Dysfunction**

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of amoxicillin/clavulanate potassium (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 reported to occur in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects. Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

***Clostridium difficile* Associated Diarrhea (CDAD)**

*Clostridium difficile* associated diarrhea (CDAD) / antibiotic-associated colitis has been reported with use of nearly all antibacterial agents, including amoxicillin/clavulanate potassium, and may range in severity from mild diarrhea to fatal colitis (mild to life threatening). Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued and a physician be consulted and an appropriate therapy initiated. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile* and surgical evaluation should be instituted as clinically indicated. Anti-peristaltic medicinal products are contraindicated in this situation.

**Potential for Microbial Overgrowth**

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfections occur, amoxicillin/clavulanate potassium should be discontinued and/or appropriate therapy instituted.

**Development of Drug-Resistant Bacteria**

Prescribing amoxicillin/clavulanate potassium in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient, and increases the risk of the development of drug-resistant bacteria.

**Skin Rash in Patients with Mononucleosis**

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash / morbilliform rash. Thus, amoxicillin/clavulanate potassium should not be administered to patients with mononucleosis.

**Allopurinol**

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

**Feverish Generalised Erythema / Acute Generalised Exanthemous Pustulosis (AGEP)**

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 amoxicillin/clavulanate potassium discontinuation and contraindicates any subsequent administration of amoxicillin.

**Convulsions**

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

**Prolongation of Prothrombin Time**

Prolongation of prothrombin time has been reported 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.

**Renal Impairment and Crystalluria**

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 reported 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.

**Interference with Laboratory Tests**

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 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.

**Other Warnings and Precautions**

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

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/formulation of amoxicillin/clavulanate potassium is not suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation/formulation should not be used to treat penicillin-resistant *S. pneumoniae*.

*Patient Counseling Information*

Patients should be informed that each dose should be taken with a meal or snack to reduce the possibility of gastrointestinal upset.

Patients should be counseled that antibacterial drugs, including amoxicillin/clavulanate potassium, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When amoxicillin/clavulanate potassium is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by amoxicillin/clavulanate potassium or other antibacterial drugs in the future.

Counsel patients that diarrhea is a common problem caused by antibacterials, and it usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken their last dose of the antibacterial. If diarrhea is severe or lasts more than 2 or 3 days, patients should contact their physician.

Patients should follow the doctor’s instructions about the amount to use and the days of treatment. Patients should discard any unused medicine.

Patients should be aware that amoxicillin/clavulanate potassium contains a penicillin class drug product that can cause allergic reactions in some individuals.

## 4.5 Interaction with other medicinal products and other forms of interaction [1, 2]

**Probenecid**

Probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of clavulanic acid. Concurrent use with amoxicillin/clavulanate potassium may result in increased and prolonged blood concentrations of amoxicillin. Co-administration of probenecid is not recommended.

**Oral Anticoagulants**

Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and oral anticoagulants (e.g. acenocoumarol or warfarin). Appropriate monitoring (including of prothrombin time or international normalized ratio) should be undertaken, when anticoagulants are prescribed concurrently and with the addition or withdrawal of amoxicillin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

**Allopurinol**

The concurrent administration of allopurinol and amoxicillin increases the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients.

**Oral Contraceptives**

Amoxicillin/clavulanate may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

**Methotrexate**

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

**Mycophenolate mofetil**

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) 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.

**Effects on Laboratory Test**

High urine concentrations of amoxicillin may result in false-positive reactions when testing for the presence of glucose in urine using alkaline copper sulfate reagent tablets, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin/clavulanate potassium, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been reported.

## 4.6 Pregnancy and lactation [1, 2]

***Pregnancy***

No evidence of harm to the fetus due to amoxicillin/clavulanate potassium has been reported in pregnant rats and mice receiving amoxicillin/clavulanate potassium (2:1 ratio formulation of amoxicillin:clavulanate) at oral doses up to 1200 mg/kg/day. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

In women with preterm, premature rupture of the fetal membrane, it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates.

*Labor and delivery*

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. It is not known whether use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

***Lactation***

Both substances reportedly 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 mucus membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman

## 4.7 Effects on ability to drive and use machines [2]

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 [1, 2]

The most commonly reported adverse drug reactions (ADRs) were diarrhea, nausea and vomiting.

The adverse drug reactions presented in below table have been derived from reported clinical studies and post-marketing surveillance data with amoxicillin and clavulanate potassium.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data)

| **Infections and infestations** | |
|---|---|
| Mucocutaneous candidosis | Common |

| | |
|---|---|
| Overgrowth of non-susceptible organisms | Not known |
| **Blood and lymphatic system disorders** | |
| Reversible leucopenia (including neutropenia) | Rare |
| Thrombocytopenia | Rare |
| Reversible agranulocytosis | Not known |
| Haemolytic anaemia | Not known |
| Prolongation of bleeding time and prothrombin time[1] | Not known |
| **Immune system disorders[10]** | |
| Angioneurotic oedema | Not known |
| Anaphylaxis | Not known |
| Serum sickness-like syndrome | Not known |
| Hypersensitivity vasculitis | Not known |
| **Nervous system disorders** | |
| Dizziness | Uncommon |
| Headache | Uncommon |
| Reversible hyperactivity | Not known |
| Convulsions[2] | Not known |
| Aeseptic meningitis | Not known |
| **Gastrointestinal disorders** | |
| Diarrhoea | Very common |
| Nausea[3] | Common |
| Vomiting | Common |
| Indigestion | Uncommon |
| Antibiotic-associated colitis[4] | Not known |
| Black hairy tongue | Not known |
| **Hepatobiliary disorders** | |
| Rises in AST and/or ALT[5] | Uncommon |
| Hepatitis[6] | Not known |
| Cholestatic jaundice[6] | Not known |
| **Skin and subcutaneous tissue disorders[7]** | |
| 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)[9] | Not known |
| Drug reaction with eosinophilia and systemic symptoms (DRESS) | Not known |
| **Renal and urinary disorders** | |

| | |
|---|---|
| Interstitial nephritis | Not known |
| Crystalluria[8] | Not known |

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanate potassium at the start of a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] A moderate rise in AST and/or ALT has been reported in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been reported with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.4
[10] See section 4.3 and 4.4

Other reported adverse reactions were vaginitis, abdominal discomfort, flatulence, diaper area rashes, gastritis, stomatitis, glossitis, enterocolitis, increase in serum bilirubin, and/or alkaline phosphatase, hematuria, anemia, thrombocytopenic purpura, eosinophilia, thrombocytosis, agitation, anxiety, behavioral changes, confusion, insomnia and tooth discoloration (brown, yellow, or gray staining). Discoloration was reported to be reduced or eliminated with brushing or dental cleaning in most cases.

## 4.9 Overdose [1, 2]

In the case of overdosage, discontinue amoxicillin/clavulanate potassium, treat symptomatically, and institute supportive measures as required. It has been reported in pediatric patients that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin/clavulanate potassium.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained. Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin/clavulanate potassium overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin/clavulanate potassium crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin/clavulanate potassium. Amoxicillin/clavulanate

potassium may be removed from circulation by hemodialysis (see section 4.2). Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

## 5. PHARMACOLOGICAL PROPERTIES [1, 2]

### 5.1 Pharmacodynamic properties

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

**Mechanism of action**
Amoxicillin is 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.

***Microbiology***

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many Gram-positive and Gram-negative bacteria. Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate some beta-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid protects amoxicillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin.

Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections.

Gram-Positive bacteria
*Staphylococcus aureus*

Gram-Negative bacteria
*Enterobacter* species
*Escherichia coli*
*Haemophilus influenzae*
*Klebsiella* species
*Moraxella catarrhalis*

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, the efficacy of amoxicillin/clavulanic acid in treating clinical infections due to these bacteria **has not been** established in adequate and well-controlled clinical trials.

Gram-Positive bacteria
*Enterococcus faecalis*

*Staphylococcus epidermidis*
*Staphylococcus saprophyticus*
*Streptococcus pneumoniae*
*Streptococcus pyogenes*
Viridians group *Streptococcus*

Gram-Negative bacteria
*Eikenella corrodens*
*Proteus mirabilis*

Anaerobic Bacteria
*Bacteroides* species, including *Bacteroides fragilis*
*Fusobacterium* species
*Peptostreptococcus* species

## 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 optimized 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 ($T_{max}$) in each case is approximately one hour.

It has been reported that, 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 to 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 reported to be 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 reported animal studies, there is no evidence for significant tissue retention of drug-derived material for either component of co-amoxiclav. 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 reported studies have found the urinary excretion to be 50 to 85% for amoxicillin and between 27 to 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.

***Pharmacokinetics in Special Populations***

*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 [1, 2]

No special hazard has been reported for humans, based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies with amoxicillin/clavulanic acid in dogs have reported gastric irritancy and vomiting, and discoloured tongue.

***Carcinogenicity / Mutagenicity / Impairment of Fertility***

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Amoxicillin/clavulanate potassium (4:1 ratio formulation of amoxicillin:clavulanate) was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin/clavulanate potassium was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin/clavulanate potassium was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays.

No effect on fertility and reproductive performance has been reported in rats receiving amoxicillin/clavulanate potassium (2:1 ratio formulation of amoxicillin:clavulanate) at

oral doses of up to 1200 mg/kg/day. Based on body surface area, this dose of amoxicillin is approximately 4 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, the dose multiple is approximately 9 times higher than the maximum recommended adult human oral dose (125 mg every 8 hours), also based on body surface area.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose, sodium starch glycollate (Type A), colloidal silicon dioxide, povidone (PVP K30), eudragit E 100, isopropyl alcohol, magnesium stearate

Film coating material-
Opadry 03B58965 White, polyethylene glycol-400, isopropyl alcohol, methylene chloride.

**6.2 Incompatibilities:** not applicable

**6.3 Shelf life:** 24 months

**6.4 Special Precautions for storage:** Store below 30°C, protected from light and moisture.

**6.5 Nature and contents of container:** The tablets are packed in PVC/PVdC blister pack in 4 layered laminated bag (marketable pack) with 10s pack size.

**6.6 Instructions for use and handling:** not applicable

## 7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Limited

## 8. MARKETING AUTHORISATION NUMBER:

Enhancin 375mg- 04-7730
Enhancin 625mg-04-2105
Enhancin 1g- 04-9025

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

January 2024

## REFERENCES


1. Prescribing Information of **AUGMENTIN®** (amoxicillin/clavulanate potassium) Tablets, Powder for Oral Suspension and Chewable Tablets, Dr. Reddy's Laboratories Inc, January, 2013.
2. Summary of Product Characteristics of **AUGMENTIN 625 mg tablets**, GlaxoSmithKline UK, December 2021.


*Information compiled in January 2024*