For the use of a Registered Medical Practitioner or a Hospital or a Laboratory or a Specialist only

Amoxycillin and Potassium Clavulanate Tablets IP 625 mg

Paxclav™ 625
TABLETS

COMPOSITION :
Each film coated tablet contains:
Amoxycillin Trihydrate IP
eq. to Amoxycillin 500 mg
Potassium Clavulanate Diluted IP
eq. to Clavulanic Acid 125 mg
Colour : Titanium Dioxide IP

DOSAGE FORM
Film Coated Tablet

THERAPEUTIC INDICATION
Amoxycillin/Potassium Clavulanate is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxycillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics.
Amoxycillin/Potassium Clavulanate should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data. It is indicated for short-term treatment of bacterial infections at the following sites:
For the treatment of bacterial infections such as sinusitis otitis media, tonsillitis, acute and chronic bronchitis, skin and soft tissue infections, pelvic infections, osteomyelitis, post-operative pain.
Susceptibility to Amoxycillin/Potassium Clavulanate will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

DOSAGE AND ADMINISTRATION
Posology
Dosage depends on the age and renal function of the patient and the severity of the infection.
Treatment should not be extended beyond 14 days without review. Therapy can be started parenterally and continued with an oral preparation.
To minimize potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Amoxycillin/Potassium Clavulanate is optimized when taken at the start of a meal.
Adults and Children over 12 years:
The usual adult dose is one Amoxycillin/Potassium Clavulanate Tablet (625 mg) every 12 hours or as directed by the Physician.
The usual recommended daily dosage is:

Mild to Moderate Infections	One Amoxycillin/Potassium Clavulanate 625 mg Tablet every 12 hours
Severe Infections	One Amoxycillin/Potassium Clavulanate 625 mg Tablet every 8 hours (thrice a day).

Amoxycillin/Potassium Clavulanate 625 mg Tablet is not recommended in children aged 12 years and below.

Special populations:
Renal impairment:
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/min, should not receive the 1g tablet.

Mild impairment (Creatinine clearance >30 mL/min)	No change in dosage
Moderate impairment (Creatinine clearance 10-30 mL/min)	One Amoxycillin/Potassium Clavulanate 625 mg Tablet twice a day
Severe impairment (Creatinine clearance <10 mL/min)	Not more than one Amoxycillin/Potassium Clavulanate 625 mg Tablet every 24 hours

Haemodialysis patients should receive an Amoxycillin/Potassium Clavulanate 625 mg Tablet every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis (as serum concentrations of both amoxycillin and clavulanic acid are decreased).
Hepatic Impairment:
Dose with caution; monitor hepatic function at regular intervals.
Pediatric Patients:
Based on the Amoxycillin component, Amoxycillin/Potassium Clavulanate should be dosed.
Patients Weighing 40 kg or more: Pediatric patients weighing 40 kg or more should be dosed according to adult recommendations.

Method of administration: For oral use only.
Amoxycillin/clavulanate potassium may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Amoxycillin/clavulanate potassium is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, Amoxycillin/clavulanate potassium should be taken at the start of a meal.
Patients should be instructed to consumed or swallow the Amoxycillin/clavulanate potassium Tablets as whole and must not to be chewed or broken.

CONTRAINDICATIONS
It is contraindicated in patients with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to Amoxycillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).
Amoxycillin/clavulanate potassium Tablet is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Amoxycillin/clavulanate potassium.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity Reactions
Serious, and occasionally fatal, hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including Amoxycillin/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. Before initiating therapy with Amoxycillin/clavulanate potassium, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, Amoxycillin/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 Amoxycillin/clavulanate potassium. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.
Clostridium difficile Associated Diarrhoea (CDAD)
Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including Amoxycillin/clavulanate potassium, and may range in severity from mild diarrhoea to fatal colitis. 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 a colectomy. CDAD must be considered in all patients who present with diarrhoea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, on-going antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
Skin Rash in Patients with Mononucleosis
A high percentage of patients with mononucleosis who receive amoxycillin develop an erythematous skin rash. Thus, Amoxycillin/clavulanate potassium should not be administered to patients with mononucleosis.
Potential for Microbial Overgrowth
The possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfection occurs, amoxycillin/clavulanate potassium should be discontinued and appropriate therapy instituted.
Development of Drug-Resistant Bacteria
Prescribing Amoxycillin/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.

DRUG INTERACTIONS
Probenecid
Probenecid decreases the renal tubular secretion of amoxycillin but does not delay renal excretion of clavulanic acid. Concurrent use with Amoxycillin/clavulanate potassium may result in increased and prolonged blood concentrations of amoxycillin. Co-administration of probenecid is not recommended.
Oral Anticoagulants
Abnormal prolongation of prothrombin time (increased international normalized ratio) has been reported in patients receiving amoxycillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently with Amoxycillin/clavulanate potassium. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
Allopurinol
The concurrent administration of allopurinol and amoxycillin increases the incidence of rashes in patients receiving both drugs as compared with patients receiving amoxycillin alone. It is not known whether this potentiation of amoxycillin rashes is due to allopurinol or the hyperuricaemia present in these patients.
Oral Contraceptives
Co-amoxyclav may affect intestinal flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral oestrogen/progesterone contraceptives.
Effects on Laboratory Tests
High urine concentrations of amoxycillin may result in false-positive reactions when testing for the presence of glucose in urine using CLINITEST, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with Amoxycillin/clavulanate potassium, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.
Following administration of amoxycillin to pregnant women, a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone, and oestradiol has been noted.

USE IN SPECIAL POPULATIONS
Pregnancy
Teratogenic Effects: Pregnancy Category B.
Reproduction studies performed in pregnant rats and mice given Amoxycillin/clavulanate potassium (2:1 ratio formulation of Amoxycillin:clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to Amoxycillin/clavulanate potassium. The Amoxycillin 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.
Labor and Delivery
Oral ampicillin-class antibiotics are poorly absorbed during labor. It is not known whether use of Amoxycillin/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.
Nursing Mothers
Amoxycillin has been shown to be excreted in human milk. Amoxycillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when Amoxycillin/clavulanate potassium is administered to a nursing woman.
Pediatric Use
The safety and effectiveness of Amoxycillin/clavulanate potassium Powder for Oral Suspension and Chewable Tablets have been established in pediatric patients. Use of Amoxycillin/clavulanate potassium in pediatric patients is supported by evidence from studies of Amoxycillin/clavulanate potassium Tablets in adults with additional data from a study of Amoxycillin/clavulanate potassium Powder for Oral Suspension 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 Amoxycillin may be delayed; clavulanate elimination is unaltered in this age group. Dosing of Amoxycillin/clavulanate potassium should be modified in pediatric patients aged <12 weeks (<3 months).
Geriatric Use
Of the 3,119 patients in an analysis of clinical studies of Amoxycillin/clavulanate potassium, 32% were ≥65 years old, and 14% were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out.
This drug is known to be substantially excreted by the kidneys, 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.

Dosing in Renal Impairment
Amoxycillin is primarily eliminated by the kidneys and dosage adjustment is usually required in patients with severe renal impairment (GFR <30 mL/min).

EFFECTS ON THE 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.

UNDESIRABLE EFFECTS
Amoxycillin/Clavulanate induced Stevens - Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN).
The following are discussed in more detail in other sections of the labeling:
- Anaphylactic reactions (see Warnings and Precautions)
- Hepatic Dysfunction (see Warnings and Precautions)
- CDAD (see Warnings and Precautions).

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The most frequently reported adverse reactions were diarrhoea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). Less than 3% of patients discontinued therapy because of drug-related adverse reactions. The overall incidence of adverse reactions, and in particular diarrhoea, increased with the higher recommended dose. Other less frequently reported adverse reactions (<1%) include: Abdominal discomfort, flatulence, and headache.
In pediatric patients (aged 2 months to 12 years), 1 US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided every 12 hours) of Amoxycillin/clavulanate potassium for 10 days versus 40/10 mg/kg/day (divided every 8 hours) of Amoxycillin/clavulanate potassium for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the suspension formulations were used in this trial. Overall, the adverse reactions seen were comparable to that noted above; however, there were differences in the rates of diarrhoea, skin rashes/urticaria, and diaper area rashes.

Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following have been identified during postmarketing use of Amoxycillin/clavulanate potassium. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Amoxycillin/clavulanate potassium.
Gastrointestinal: Indigestion, gastritis, stomatitis, glossitis, black 'hairy' tongue, mucocutaneous candidiasis, enterocolitis, and haemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.
Hypersensitivity Reactions: Pruritus, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, StevensJohnson syndrome, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and cases of exfoliative dermatitis (including toxic epidermal necrosis) have been reported.
Liver: Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with Amoxycillin/clavulanate potassium. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. Deaths have been reported.
Renal: Interstitial nephritis, haematuria, and crystalluria have been reported.
Haemic and Lymphatic Systems: Anaemia, including haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Thrombocytosis was noted in less than 1% of the patients treated with Amoxycillin/clavulanate potassium. There have been reports of increased prothrombin time in patients receiving Amoxycillin/clavulanate potassium and anticoagulant therapy concomitantly.
Central Nervous System: Agitation, anxiety, behavioural changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported.
Miscellaneous: Tooth discolouration (brown, yellow, or grey staining) has been reported. Most reports occurred in paediatric patients. Discolouration was reduced or eliminated with brushing or dental cleaning in most cases.

OVERDOSE
In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. A prospective study of 51 paediatric patients at a poison-control centre suggested that overdosages of less than 250 mg/kg of amoxycillin are not associated with significant clinical symptoms.
Interstitial nephritis resulting in oliguric renal failure has been reported in patients after overdosage with amoxycillin/clavulanate potassium.
Crystalluria, in some cases leading to renal failure, has also been reported after amoxycillin/clavulanate potassium overdosage in adult and paediatric patients.
In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxycillin/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 amoxycillin/clavulanate potassium. Amoxycillin/clavulanate potassium may be removed from circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES
Mechanism of Action
Amoxycillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. Amoxycillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxycillin alone does not include organisms which produce these enzymes.
Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms 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. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.
The presence of clavulanic acid in amoxycillin-clavulanate formulations protects amoxycillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxycillin to include many bacteria normally resistant to amoxycillin and other penicillins and cephalosporins. T hus amoxycillin-clavulanate possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacodynamic Properties
Amoxycillin is a semisynthetic antibiotic with in vitro bactericidal activity against Gram-positive and gram-negative bacteria. Amoxycillin is, however, susceptible to degradation by beta-lactamases and, therefore, the spectrum of activity does not include organisms that produce these enzymes. 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.
Amoxycillin/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% of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxycillin/clavulanic acid. However, the efficacy of amoxycillin/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
Viridans group Streptococcus
Gram-negative Bacteria
Eikenella corrodens
Proteus mirabilis
Anaerobic Bacteria
Bacteroides species, including *Bacteroides fragilis*
Fusobacterium species
Peptostreptococcus species

Pharmacokinetic properties
Mean Amoxycillin and clavulanate potassium pharmacokinetic parameters in normal adults following administration of Amoxycillin/clavulanate potassium Tablets are shown in below Table-1.
Table-1: Mean (±S.D.) Amoxycillin and Clavulanate Potassium Pharmacokinetic Parameters[a,b] with Amoxycillin/clavulanate potassium Tablets

Dose and Regimen	Cmax (mcg/mL)		AUC0-24 (mcg*h/mL)	
Amoxycillin/Clavulanate Potassium	Amoxycillin	Clavulanate Potassium	Amoxycillin	Clavulanate Potassium
250/125 mg every 8 hours	3.3 ± 1.12	1.5 ± 0.70	26.7 ± 4.56	12.6 ± 3.25
500/125 mg every 12 hours	6.5 ± 1.41	1.8 ± 0.61	33.4 ± 6.76	8.6 ± 1.95
500/125 mg every 8 hours	7.2 ± 2.26	2.4 ± 0.83	53.4 ± 8.87	15.7 ± 3.86

[a] Mean (± standard deviation) values of 14 normal adults (N=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
[b] Amoxycillin/clavulanate potassium administered at the start of a light meal.
Amoxycillin serum concentrations achieved with Amoxycillin/clavulanate potassium are similar to those produced by the oral administration of equivalent doses of Amoxycillin alone. Time above the minimum inhibitory concentration of 1 mcg/mL for Amoxycillin has been shown to be similar after corresponding every 12 hour and every 8 hour dosing regimens of Amoxycillin/clavulanate potassium in adults and children.
Absorption
Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of Amoxycillin. While Amoxycillin/clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when Amoxycillin/clavulanate potassium was dosed at 30 and 150 minutes after the start of a high-fat breakfast.
Distribution
Neither component in Amoxycillin/clavulanate potassium is highly protein-bound; clavulanic acid is approximately 25% bound to human serum and Amoxycillin approximately 18% bound.
Amoxycillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid.
Metabolism and Excretion
The half-life of Amoxycillin after the oral administration of Amoxycillin/clavulanate potassium is 1.3 hours and that of clavulanic acid is 1 hour.
Approximately 50% to 70% of the Amoxycillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250-mg or 500-mg tablet of Amoxycillin/clavulanate potassium.

INCOMPATIBILITIES
None stated.

STORAGE INSTRUCTIONS
Store protected from moisture, at a temperature not exceeding 25°C.

Keep all medicines out of reach of children.

Manufactured by : Malik Lifesciences Pvt. Ltd.
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