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

ENHANCIN

TABLETS

(Amoxicillin and Clavulanate Potassium Tablets USP)

COMPOSITION

ENHANCIN 375 mg Tablets
Each film-coated tablet contains

Amoxicillin USP equivalent to anhydrous Amoxicillin	250 mg
Clavulanate Potassium equivalent to Clavulanic Acid	125 mg

ENHANCIN 625 mg Tablets
Each film-coated tablet contains

Amoxicillin USP equivalent to anhydrous Amoxicillin	500 mg
Clavulanate Potassium equivalent to Clavulanic Acid	125 mg

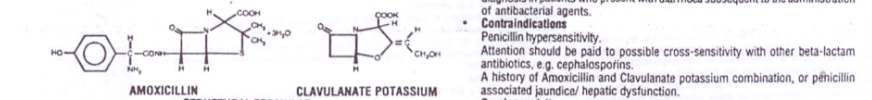
ENHANCIN 1 g Tablets
Each film-coated tablet contains

Amoxicillin USP equivalent to anhydrous Amoxicillin	875 mg
Clavulanate Potassium equivalent to Clavulanic Acid	125 mg

DESCRIPTION

ENHANCIN is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the beta-lactamase inhibitor potassium clavulanate providing a broad spectrum of antibacterial activity against beta-lactamase producing bacteria. Amoxicillin is chemically designated as (6R)-6-alpha-D-(4Hydroxyphenyl) -glycylamino penicillanic acid trihydrate.Its empirical formula is $C_{16}H_{19}N_3O_5S.3H_2O$. Its molecular weight is 419.5.

Potassium clavulanate is chemically designated as Potassium(Z)-(2R,5R)-3-(-Hydroxyethylidene)- 7 oxo-4-oxa- 1azabicyclo (3.2.0) heptane-2-carboxylate.Its empirical formula is $C_8H_8NO_5K$ and its molecular weight is 237.3.



AMOXICILLIN CLAVULANATE POTASSIUM
STRUCTURAL FORMULAE

PHARMACOLOGY[1,2,3,4]

- **Mechanism of Action**
  Amoxicillin acts through inhibition of biosynthesis of the bacterial cell wall mucopeptide. It is bactericidal against many Gram-positive and Gram-negative organisms. However, being susceptible to degradation by b-lactamases, its spectrum does not include b- lactamase producing bacteria. Clavulanic acid inhibits a wide range of bacterial b-lactamases and protects amoxicillin from degradation by b-lactamase enzymes and effectively extends the antibacterial spectrum of Amoxicillin to include many b-lactamase producing strains of bacteria.
- **Antibacterial Spectrum**
  The following pathogens have been found to be susceptible to Amoxicillin and Clavulanate potassium combination:
  Gram-positive
  Aerobes: *Enterococcus faecalis, Enterococcus faecium, Strep. pneumoniae, Strep. pyogenes, Strep. viridans, Staphylococcus aureus* *, coagulase negative staphylococci* (including Staph. epidermidis *), Corynebacterium spp., Bacillus anthracis, Listeria monocytogenes.*
  Anaerobes: Clostridium spp., Peptococcus spp., Peptostreptococcus spp.
  Gram-negative
  Aerobes: *H. influenzae *, E.coli *, Pr. mirabilis *, Pr. vulgaris **, Klebsiella spp.*, *Moraxella catarrhalis* (Branhamella catarrhalis)*, Salmonella spp.*, Shigella spp.*, *Bordetella pertussis*, Brucella spp., *N. gonorrhoeae *, N. meningitidis, Vibrio cholerae, Pasteurella multocida.*
  Anaerobes: Bacteroides spp.* (including *B. fragilis*.), Fusobacterium spp.*
  * including beta-lactamase producing strains
- **Pharmacokinetics**
  Amoxicillin and Clavulanate potassium are both well absorbed after oral administration and are stable in the presence of gastric acid. Food does not affect the absorption of Amoxicillin and this combination product may be given without regard to meals. However, administration at the start of a meal improves the absorption of Clavulanate and minimises the potential for gastrointestinal intolerance. The oral bioavailability of Amoxicillin and Clavulanate potassium is approximately 90% and 75% respectively.
  Clavulanate potassium has about the same plasma elimination half-life (1hr) as that of amoxicillin (1.3 hrs).
  Amoxicillin and Clavulanic acid are widely distributed to most tissues and body fluids including peritoneal fluid, blister fluid, urine, pleural fluid, middle ear fluid, intestinal mucosa, bone, gallbladder, lung, female reproductive tissues and bile. Penetration into CSF through non-inflammed meninges and into purulent bronchial secretions is low. Amoxicillin and Clavulanic acid readily cross the placenta and are secreted into breast milk in low concentrations.
  Amoxicillin is bound to serum proteins to an extent of 17-20% while Clavulanic acid is 20-30% bound to serum proteins. Approximately 10% of the dose of Amoxicillin and less than 50% of dose of Clavulanate are metabolised.
  Amoxicillin and Clavulanate potassium combination is eliminated primarily unchanged through the renal route (glomerular filtration and tubular secretion). Approximately 50-70% of Amoxicillin and 25-40% of Clavulanic acid are excreted unchanged in urine within the first 6 hrs. after administration.
  Mean* Amoxicillin and Clavulanate potassium pharmacokinetic parameters are shown in the table below:

Dose** and regimen	$AUC_{0\text{-}24}$ ($\mu g.h/ml$)		C_{max} ($\mu g/ml$)	
Amoxicillin/ Clavulanate potassium (±SD)	Amoxicillin (±SD)	Clavulanate potassium (±SD)	Amoxicillin (±SD)	Clavulanate potassium (±SD)
250/125 mg q 8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q 12h	33.4 ± 5.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q 8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 mg q 12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

* Mean values of 14 normal volunteers (n=15 for Clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
** Administered at the start of a light meal

INDICATIONS[3,4]

ENHANCIN tablets are indicated for the treatment of following infections caused by susceptible pathogens:

i) Upper respiratory tract infections(including otorhinolaryngeal) e.g. sinusitis, otitis media, tonsillitis
ii) Lower respiratory tract infections (e.g. lobar and bronchopneumonia, acute and chronic bronchitis)
iii) Genito-urinary tract infections (e.g. cystitis, urethritis, pyelonephritis)
iv) Skin and soft tissue infections (e.g. boils, abscesses, cellulitis, wound infections)
vi) Dental infections (e.g. dentoalveolar abscess)
vii) Other infections (e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis)

DOSAGE & ADMINISTRATION[3,4]

Adults
The usual adult dose is 1 **ENHANCIN** 625 mg tablet every 12 hrs or 1 **ENHANCIN** 375 mg tablet every 8 hrs.
For more severe infections and infections of the respiratory tract, the dose should be 1 **ENHANCIN** 1 g tablet every 12 hrs or 1 **ENHANCIN** 625 mg tablet every 8 hrs.
Dosage in dental infections
Adults and children over 12 years: One **ENHANCIN** 375 mg tablet three times a day for five days.
Other infections (e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis)
The usual dose for adults and children over 12 years is one **ENHANCIN** 375 mg tablet three times a day. In severe infections one **ENHANCIN** 625 mg tablet three times a day is recommended. Therapy can be started parenterally and continued with an oral preparation.
Dosage in Renal Impairment
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with glomerular filtration rate of < 30 ml /minute should not receive **ENHANCIN** 1 g tablet. Patients with a glomerular filtration rate of 10-30 ml/minute should receive **ENHANCIN** 625 mg or **ENHANCIN** 375 mg every 12 hrs, depending on the severity of the infection. Patients with a less than 10 ml/minute glomerular filtration rate should receive **ENHANCIN** 625 mg or **ENHANCIN** 375 mg every 24 hrs, depending on the severity of the infection.
Haemodialysis patients should receive **ENHANCIN** 625 mg or **ENHANCIN** 375 mg every 24 hrs, depending on the severity of the infection. They should receive an additional dose both during and at the end of dialysis.
Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.
Paediatric patients
Paediatric patients weighing 40 kg or more should be dosed according to adult recommendation.

Oral administration
Tablets should be swallowed whole without chewing. If required, tablets may be broken in half and swallowed without chewing.
To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Amoxicillin and Clavulanate potassium combination is optimised when taken at the start of a meal.
Treatment should not be extended beyond 14 days without review.

PRECAUTIONS[2,3,4]

- **General**
  Amoxicillin and Clavulanate potassium combination should be used with caution in patients with evidence of severe hepatic dysfunction; change in liver function tests have been observed in some patients receiving this combination.
  Erythematous rashes have been associated with glandular fever in patients receiving Amoxicillin.
  The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and appropriate therapy instituted.
- **Warnings**
  Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on β-lactam therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens; careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the Amoxicillin and Clavulanate potassium combination should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.
  Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Amoxicillin and Clavulanate potassium combination and has ranged in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
- **Contraindications**
  Penicillin hypersensitivity.
  Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics, e.g. cephalosporins.
  A history of Amoxicillin and Clavulanate potassium combination, or penicillin associated jaundice/ hepatic dysfunction.
- **Carcinogenicity**
  Long-term carcinogenicity studies in animals have not been performed with Amoxicillin and Clavulanate potassium combination.
- **Mutagenicity**
  The mutagenic potential of Amoxicillin and Clavulanate potassium combination was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
- **Pregnancy and Lactation**
  Reproduction studies in animals (mice and rats) with orally and parenterally administered Amoxicillin and Clavulanate potassium combination have shown no teratogenic effects. There is limited experience of the use of Amoxicillin and Clavulanate potassium combination in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.
  Amoxicillin and Clavulanate potassium combination may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.
- **Paediatrics**
  Paediatric patients weighing 40 kg or more should be dosed according to adult recommendation (see **DOSAGE AND ADMINISTRATION**).
- **Geriatrics**
  Penicillins have been used in geriatric patients and no geriatrics-specific problems have been documented to date. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment in dosage in patients receiving penicillins.
- **Drug Interactions**
  Prolongation of bleeding time and prothrombin time may occur in some patients receiving Amoxicillin and Clavulanate potassium combination. This combination should be used with caution in patients receiving anti-coagulant therapy.
  An increased incidence of rash may occur in patients with hyperuricemia who are receiving allopurinol and concomitant Amoxicillin or Ampicillin.
  In common with other broad-spectrum antibiotics, Amoxicillin and Clavulanate potassium combination may reduce the efficacy of oral contraceptives.
  Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of Amoxicillin. Concomitant use with Amoxicillin and Clavulanate potassium combination may result in increased and prolonged blood levels of Amoxicillin but not of Clavulanic acid.
- **Laboratory value alterations**
  Urine glucose test: High urinary concentrations of a penicillin may produce false-positive or falsely elevated test results with copper-reduction test [Benedict's, Clinitest, or Fehling's]. Glucose enzymatic tests [Clinistix or Testape] are not affected.
- **Adverse Effects**
  Side effects with Amoxicillin and Clavulanate potassium combination are uncommon and mainly of a mild and transitory nature.
  Reported side effects include diarrhoea, indigestion, nausea, vomiting and mucocutaneous candidiasis.
  Occasionally moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases; and rarely hepatitis and cholestatic jaundice have been reported to occur. Signs and symptoms may occur during treatment but are more frequently reported after cessation of therapy with a delay of upto 6 weeks.
  Urticaria and erythematous rashes have been reported occasionally.
  Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, serum sickness like syndrome, hypersensitivity vasculitis, interstitial nephritis, pseudomembranous colitis, prolongation of bleeding time and prothrombin time have been reported to occur rarely.
  In common with other beta-lactam antibiotics, angioedema and anaphylaxis, transient leucopenia, thrombocytopenia and haemolytic anaemia have been reported rarely.
  Side effects involving the CNS which include reversible hyperactivity, dizziness, headache and convulsions may occur very rarely.

OVERDOSAGE[3,4]

Overdosage with Amoxicillin and Clavulanate potassium combination is unlikely to occur. Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically with attention to the water electrolyte balance.
Amoxicillin and Clavulanate combination may be removed from the circulation by haemodialysis.

STORAGE

Store below 25°C, protected from moisture.
KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.
"THIS DRUG IS REGISTERED IN LIST 1"

SUPPLY

ENHANCIN 375 mg TABLETS:
Blister of 10's, Box of 10's/10 x 10's and 20's/5 x 20's.
ENHANCIN 625 mg TABLETS:
Blister of 10's, Box of 10's/10 x 10's and 20's/5 x 20's.
ENHANCIN 1 g TABLETS:
Strip of 2's and box of 6 x 2's

REFERENCES

1. Martindale – The Complete Drug Reference 1999; 32nd Ed: 151-53, 190-91.
2. USPDI Drug Information for the Health Care Professional 1996; 16th Ed.: 2301-2330.
3. Physicians' Desk Reference 2001; 55th Ed.: 3068-71.
4. ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000: 1587-88.

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