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

ENHANCIN INJECTION

(Clavulanate Potassium and Amoxicillin Injection)

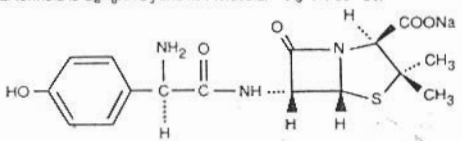
COMPOSITION

ENHANCIN INJECTION 300 mg
Each vial contains :
Clavulanate Potassium (Sterile) USP
equivalent to Clavulanic Acid 50 mg
Amoxicillin Sodium (Sterile) Ph. Eur.
equivalent to Amoxicillin 250 mg

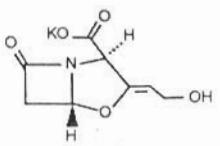
ENHANCIN INJECTION 1.2 g
Each vial contains :
Clavulanate Potassium (Sterile) USP
equivalent to Clavulanic Acid 200 mg
Amoxicillin Sodium (Sterile) Ph. Eur.
equivalent to Amoxicillin 1000 mg

DESCRIPTION

ENHANCIN is an antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the beta-lactamase inhibitor clavulanate potassium resulting in a broad spectrum of antibacterial activity.
Amoxicillin Sodium is chemically designated as Sodium (2S,5R,6R)-6-[[(2R)-2- amino-2-(4-hydroxyphenyl) acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate. Its empirical formula is $C_{16}H_{18}N_3NaO_5S$ and its molecular weight is 387.4.
Clavulanate Potassium is chemically designated as Potassium (Z)-(2R,5R)-3- (-2-hydroxyethylidene) -7-oxo-4-oxa-1-azabicyclo [3.2.0] heptane-2-carboxylate. Its empirical formula is $C_8H_8KNO_5$ and its molecular weight is 237.25.



AMOXICILLIN SODIUM



CLAVULANATE POTASSIUM

STRUCTURAL FORMULAE

PHARMACOLOGY

Mechanism of Action[1]

Amoxicillin acts through inhibition of biosynthesis of the bacterial cell wall mucopeptide. It is bactericidal against many Gram-positive and Gram-negative organisms during the stage of active multiplication. However, it is susceptible to degradation by beta-lactamases and therefore its spectrum does not include beta-lactamase producing bacteria. Clavulanic acid is a beta-lactam structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamases commonly found in bacteria resistant to beta-lactam antibiotics.
The formulation of amoxicillin with clavulanic acid protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other beta-lactam antibiotics.

Antibacterial Spectrum[2]

The following pathogens have been found to be susceptible to Amoxicillin and Clavulanate Potassium combination :

Gram-positive bacteria :
Aerobes
*Staphylococcus aureus**
*Staph. epidermidis**
*Staph. saprophyticus**
Strep. pyogenes
Strep. pneumoniae
Strep. viridans
Enterococcus faecalis
Bacillus anthracis
Corynebacterium spp.
Listeria monocytogenes
Anaerobes
Clostridia spp.
Peptococcus spp.
Peptostreptococcus spp.
Anaerobes
Bacteroides including *B.fragilis**

Gram-negative bacteria :
Aerobes
*E. coli**
*Pr. vulgaris**
*Pr. mirabilis**
Klebsiella spp.
Salmonella spp.
Shigella spp.
Bordetella pertussis
Brucella spp.
*N. gonorrhoeae**
*Moraxella catarrhalis**
*H. influenzae**
Pasteurella multocida
Vibrio cholerae
*Legionella Spp.**

*includes both beta lactamase and non-beta lactamase producing.

Pharmacokinetics[2,3,4]

The pharmacokinetics of amoxicillin and clavulanate potassium are closely matched.
Clavulanic acid 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 distributed into breast milk in low concentrations. Amoxicillin is bound to serum proteins to an extent of 17-20% while clavulanic acid is 22-30% 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 50-78% of amoxicillin and 25-40% of clavulanic acid are excreted unchanged in urine within the first 6 hours after administration.

INDICATIONS[3]

ENHANCIN INJECTION is indicated for the treatment of following infections caused by susceptible pathogens :
i) Lower respiratory tract infections (e.g. lobar- and broncho-pneumonia, acute and chronic bronchitis).
ii) Upper respiratory tract infections (including ENT) e.g. sinusitis, otitis media, tonsillitis.
iii) Genito-urinary and abdominal infections e.g. cystitis, urethritis, pyelonephritis, female genital infections, pelvic or puerperal sepsis, septic abortion, intra-abdominal sepsis, peritonitis.
iv) Skin and soft tissue infections e.g. cellulitis, abscesses, wound infections, boils.
v) Bone and joint infections e.g. osteomyelitis.
vi) Septicaemia.
vii) Post-surgical infections.

ENHANCIN INJECTION is also indicated in the prophylaxis against infections which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract surgery.

DOSAGE[3]

ENHANCIN INJECTION may be administered by intravenous or by intermittent infusion. IT IS NOT SUITABLE FOR INTRAMUSCULAR ADMINISTRATION.

Adults and children over 12 years : Usually **ENHANCIN INJECTION 1.2 g** 8 hourly. In more serious infections, increase frequency to 6 hourly intervals. Maximum daily adult dose should not exceed 7.2 g by IV route. Maximum single dose is 1.2 g.
Children 3 months - 12 years : Usually 30 mg/kg.* **ENHANCIN INJECTION** 8 hourly. In more serious infections, increase frequency to 6 hourly intervals.
Children 0-3 months : 30 mg/kg.* **ENHANCIN INJECTION** every 12 hours in premature infants and in full term infants during the perinatal period, increasing to 8 hours thereafter.

*Each 30 mg **ENHANCIN INJECTION** provides 5 mg clavulanic acid and 25 mg amoxicillin.
Therapy can be started parenterally and continued with an oral preparation. Treatment with **ENHANCIN INJECTION** should not extend beyond 14 days without review.

Adult dosage for surgical prophylaxis :

Usual dose : **ENHANCIN INJECTION 1.2 g** given at the induction of anaesthesia.
Operation with high risk of infection (e.g. colorectal surgery) :
ENHANCIN INJECTION 1.2 g given upto four times in a 24 hour period (usually at 0,8,16 and 24 hours). This regime can be continued for several days if the procedure has a significantly increased risk of infection.

Dosage in renal impairment :

Adults

Mild impairment (Creatinine clearance > 30 ml/min)	Moderate impairment (Creatinine clearance 10-30 ml/min)	Severe impairment (Creatinine clearance < 10 ml/min)
No change in dosage	1.2 g IV stat. followed by 600 mg IV 12 hourly.	1.2 g IV stat. followed by 600 mg IV 24 hourly. Dialysis decreases serum concentration of **ENHANCIN INJECTION** and an additional 600 mg IV dose may need to be given during dialysis and at the end of dialysis

Children : Similar reductions in dosage should be made for children.
Dosage in hepatic impairment : Dose with caution, monitor hepatic function at regular intervals.
Each 1.2 g vial of **ENHANCIN INJECTION** contains 1.0 mmol of potassium and 3.1 mmol of sodium (approx.).
Each 300 mg vial of **ENHANCIN INJECTION** contains 0.25 mmol of potassium and 0.78 mmol of sodium (approx.).

PREPARATION AND ADMINISTRATION

ENHANCIN INJECTION may be administered by intravenous or by intermittent infusion. IT IS NOT SUITABLE FOR INTRAMUSCULAR ADMINISTRATION.
Dissolve the contents of the vial in 5 ml (in case of **ENHANCIN INJECTION 300 mg**) or 20 ml (in case of **ENHANCIN INJECTION 1.2 g**) of water for injection.
ENHANCIN INJECTION should be given by slow intravenous injection over a period of three to four minutes and used within 20 minutes of reconstitution.
ENHANCIN INJECTION may be injected directly into a vein or via a drip tube.
Alternatively, **ENHANCIN INJECTION 1.2 g** may be infused in water for injection or Sodium chloride intravenous injection (0.9% w/v). Add without delay* the 1.2 g reconstituted solution to 100 ml infusion fluid. Infuse over 30-40 minutes and complete within 4 hours of reconstitution.
*Solutions should be made up to full infusion volume immediately after reconstitution. Any residual antibiotic solution should be discarded.

STABILITY AND COMPATIBILITY

Intravenous infusions of **ENHANCIN INJECTION** may be given in a range of different intravenous fluids. Satisfactory antibiotic concentrations are retained at 5°C and at room temperature (25°C) in the recommended volumes of the following infusion fluids. If reconstituted and maintained at room temperature, infusions should be completed within the time stated.
Reconstituted solutions should not be frozen.

Intravenous infusion fluids	Stability period 25°C
Water for injection	4 hours
Sodium Chloride Intravenous infusion (0.9% w/v)	4 hours
Sodium Lactate Intravenous infusion (one sixth molar)	4 hours
Compound Sodium Chloride Intravenous infusion (Ringer's Solution)	3 hours
Compound Sodium Lactate Intravenous infusion (Ringer-Lactate Solution; Hartmann's Solution)	3 hours
Potassium Chloride and Sodium Chloride Intravenous infusion	3 hours

ENHANCIN INJECTION is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solutions of **ENHANCIN INJECTION** should therefore not be added to such infusions but may be injected into the drip tubing over a period of 3-4 minutes.
For storage at 5°C, the reconstituted solution should be added to pre-refrigerated infusion bags which can be stored for upto 8 hours. Thereafter, the infusion should be administered immediately after reaching room temperature.

Intravenous infusion fluids	Stability period 5°C
Water for injection	8 hours
Sodium Chloride Intravenous infusion (0.9% w/v)	8 hours

ENHANCIN INJECTION should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If **ENHANCIN INJECTION** is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or administration set because loss of the aminoglycoside can occur under these conditions.

PRECAUTIONS

General[3,4] : ENHANCIN INJECTION 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 Amoxicillin and Clavulanic acid combination.
In patients with moderate or severe renal impairment, dose adjustment of **ENHANCIN INJECTION** is recommended (See Dosage and Administration).
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.
An adequate fluid intake and urinary output should be maintained during treatment with **ENHANCIN INJECTION** to minimise the possibility of crystalluria.
Moreover, a regular check on patency of bladder catheters may be necessary since amoxicillin may precipitate at high concentrations in urine.
Warnings[1,3] : Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity; careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Amoxicillin and Clavulanate Potassium combination. It is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
Contraindications[3] : Penicillin hypersensitivity.
Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics, e.g. cephalosporins. A history of **ENHANCIN** or penicillin associated jaundice / hepatic dysfunction.
Carcinogenicity[4] : *Long-term carcinogenicity studies in animals have not been performed with Amoxicillin and Clavulanate Potassium combination.*
Mutagenicity[4] : Long-term studies in animals have not been performed to evaluate the mutagenic potential of Amoxicillin and Clavulanate Potassium combination.
Pregnancy and Lactation[3] : No adverse effects were observed when Amoxicillin and Clavulanate Potassium combination was administered in pregnant rats and mice. However, use of **ENHANCIN INJECTION** in pregnancy is not recommended unless considered essential by the physician.
ENHANCIN INJECTION may be administered to nursing mothers; no specific adverse event other than risk of sensitisation for the infant has been reported.
Paediatrics : Many penicillins have been used in paediatric patients, and no paediatrics specific problems have been documented to date. However, the incompletely developed renal function of neonates and young infants may delay the excretion of renally eliminated penicillins.
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[3] : Prolongation of bleeding time and prothrombin time may occur in some patients receiving amoxicillin and clavulanate combination.
ENHANCIN INJECTION 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.
Adverse Effects[2,3] : Side effects with **ENHANCIN INJECTION** 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, thrombophlebitis at the site of injection 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] : Overdosage with **ENHANCIN INJECTION** is unlikely to occur, Symptomatic and supportive measures should be instituted with particular attention to the restoration of fluid and electrolyte imbalance.
Amoxicillin and clavulanate combination may be removed from the circulation by haemodialysis.

STORAGE

Store below 25°C, protected from moisture. Do not freeze.

SUPPLY

ENHANCIN INJECTION 300 mg : 5 ml vial in a carton.
ENHANCIN INJECTION 1.2 g : 20 ml vial in a carton.

Keep all medicines out of the reach of children.

REFERENCES

1) *Martindale. The Extra Pharmacopoeia, 1996, 31st ed.; 171-172, 211.*
2) *Mosby's Gen Rx. 1998, 8th ed.; II 115-II 117*
3) *ABPI Compendium of Data Sheets, 1998-99 : 148-149*
4) *Drug Information for the Health Care Professional (USPDI), 1996, 16th ed.: 2324-2331.*

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