Acknowledgement

Draft

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CLAMENTIN INJECTION 1.2G

Ingredient(s):
Each vial contains:
Amoxicillin (as Amoxicillin Sodium) ..... 1g (potency)
Clavulanic Acid (as Potassium Clavulanate) ..... 0.2g (potency)

Pharmacodynamics:
Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in Clamentin anticipates this defense mechanism by blocking the β-lactamase enzymes, thus rendering the organisms sensitive to Amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.
Clamentin is bactericidal to a wide range of organisms including:
Gram-positive:
Aerobes: **Enterococcus faecalis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, *Staphylococcus aureus,* *Coagulase-negative staphylococci (including *Staphylococcus epidermidis*), *Corynebacterium* sp, **Bacillus anthracis, Listeria monocytogenes, Enterococcus faecium, Streptococcus agalactiae, Streptococcus* sp.
Anaerobes: *Clostridium, Peptococcus* spp, Peptostreptococcus.
Gram-negative:
Aerobes: **Haemophilus influenzae, *Escherichia coli, *Proteus mirabilis, *Proteus vulgaris, *Klebsiella* sp, **Moraxella catarrhalis (Branhamella catharralis), *Salmonella* sp, **Shigella* sp, *Bordetella pertussis, Brucella* sp, **Neisseria gonorrhoeae, *Neisseria meningitidis, Vibrio cholerae, *Yersinia enterocolitica, Pasteurella multocida. Gardnerella vaginalis, Helicobacter pylori, Legionella* sp.
Anaerobes: **Bacteroides* sp (including *Bacteroides fragilis*), **Fusobacterium* sp.
* Including β-lactamase producing strains resistant to ampicillin and Amoxicillin.

Pharmacokinetics:
Amoxicillin and Potassium Clavulanate are well absorbed from the gastrointestinal tract after oral administration. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of Amoxicillin. While Clamentin can be given without regard to meals, absorption of Clavulanic Acid when taken with food is greater relative to the fasted state.
Amoxicillin serum concentrations achieved with Clamentin are similar to those produced by the oral administration of equivalent doses of Amoxicillin alone. The half-life of Amoxicillin after oral administration is 1.3 hours and that of Clavulanic Acid is 1.0 hour.
Concurrent administration of probenecid delays Amoxicillin excretion but does not delay renal excretion of Clavulanic Acid. Clavulanic Acid has been found to be approximately 25% bound to human serum and Amoxicillin approximately 18% bound. Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of Clavulanic Acid to animals suggest that this compound, like Amoxicillin, is well distributed in body tissues.

Indication(s):
Clamentin Injection 1.2g is indicated for short-term treatment of bacterial infections at the following sites when Amoxicillin-resistant β-lactamase-producing strains are suspected as the cause:
- **Upper Respiratory Tract Infections** (Including ENT) in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae, Haemophilus influenzae*, Moraxella catarrhalis** and *Streptococcus pyogenes.*
- **Lower Respiratory Tract Infections** in particular acute exacerbations of chronic bronchitis (especially if considered severe), bronchopneumonia. These infections are often caused by *Streptococcus pneumoniae, Haemophilus influenzae** and *Moraxella catarrhalis**.
- **Genito-urinary Tract and Abdominal Infections** in particular cystitis (especially when recurrent or complicated – excluding prostatitis), septic abortion, pelvic or puerperal sepsis and intra-abdominal sepsis. These infections are often caused by *Enterobacteriaceae* (mainly Escherichia coli*), Staphylococcus saprophyticus, Enterococcus species**.
- **Skin and Soft Tissue Infections** in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*, Streptococcus pyogenes* and *Bacteroides species**.
- **Prophylaxis of wound infection associated with surgical procedures** in particular gastrointestinal, pelvic, major head and neck surgery and after limb amputation for infection.

* Some member of these species of bacteria produces β-lactamase, rendering them insensitive to Amoxicillin alone.

Dosage and Administration:
Adults: By intravenous injection over 3-4 minutes or by intravenous infusion, 1.2g every 8 hours. Increased to 1.2g every 6 hours in more serious infections.
Children 3 months – 12 years: 30mg/kg every 8 hours, increased to 30mg/kg every 6 hours in more serious infections.
Children 0 – 3 months: 30mg/kg every 12 hours during the perinatal period and in premature infants, increasing to every 8 hours thereafter.
Surgical prophylaxis: 1.2g at induction; for high risk procedures (e.g. colorectal surgery) a further 2-3 doses may be given every 8 hours in a 24-hour period. Continue for several days if the procedure has a significantly increased risk of infection.
Renal Impairment:
Adults: Mild impairment (creatinine clearance >30mL/min) – no change in dosage.
Moderate impairment (creatinine clearance 10-30mL/min) – 1.2g I.V. stat, followed by 600mg I.V. 12 hourly.
Severe impairment (creatinine clearance <10mL/min) – 1.2g I.V. stat, followed by 600mg I.V. 24 hourly. An additional 600mg I.V. dose may need to be given during dialysis and at the end of dialysis.
Children: similar reductions in dosage should be made.

Route of Administration: For I.V. use only.

Preparation for injection
Clamentin Injection 1.2g may be administered either by intravenous injection or by intermittent infusion. It is not suitable for intramuscular administration.
1.2g vial: To reconstitute dissolve contents in 20mL of Water For Injection BP.

Intravenous injection:
Administer slowly, over a period of 3-4 minutes. Clamentin may be injected directly into a vein or via a drip tube. Intravenous Injections of Clamentin must be administered within 10 minutes.

Intravenous infusion:
Add 1.2g reconstituted solution to 100mL infusion fluid. The infusion should be given over 30-40 minutes. Solution should be made up to full infusion volume immediately after reconstitution.
Any residual antibiotic solutions should be discarded.

CAUTION FOR USAGE:
Stability and compatibility:
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 times stated as table below.

I.V. Infusion Fluid	Stability Period at 25°C	Stability Period at 5°C
Water for injection BP	4 hrs	8 hrs
Sodium Chloride I.V. Infusion BP (0.9% w/v)	4 hrs	

Reconstituted solutions should not be frozen.
Clamentin is less stable in infusions containing glucose, dextran or bicarbonate.
Reconstituted solutions should therefore not be added to such infusions but may be injected into the drip tubing over a period of 3-4 min.
If Clamentin I.V. is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, I.V. fluid container or given set because loss of activity of the aminoglycoside can occur under these conditions.
For storage at 5°C, the reconstituted solution should be added to pre-refrigerated infusion bags which can be stored for up to 8 hrs. Thereafter, the infusion should be administered immediately after reaching room temperature.

Contraindication(s):
1. Penicillin hypersensitivity.
2. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporin.
3. A previous history of Clamentin or penicillin-associated jaundice/hepatic dysfunction.

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Precaution(s) / Warning(s):
1. Clamentin should be used with caution in patients with evidence of hepatic dysfunction.
2. Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.
3. In patients with moderate or severe renal impairment, dosage should be adjusted.
4. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity.
5. Erythematous rashes have been associated with glandular fever in patients following the use of Amoxicillin. Clamentin should be avoided if glandular fever is suspected.
6. During the administration of high doses, adequate fluid intake and urinary output should be maintained to minimize the possibility of crystalluria.
7. Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.

Interaction with Other Medicaments:
Prolongation of bleeding time and prothrombin time may be possible. Clamentin should be used with care in patients on anti-coagulation therapy.
In common with other broad-spectrum antibiotics, Clamentin may reduce the efficacy of oral contraceptives and patients should be warned accordingly.
Concomitant use of Probenecid is not recommended. Probenecid decreases the renal tubular secretion of Amoxicillin. Concomitant use with Clamentin may result in increased and prolonged blood levels of Amoxicillin but not of Clavulanic Acid. Concomitant use of allopurinol during treatment with Amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Clamentin and allopurinol.

Pregnancy and Lactation:
1. Use in pregnancy
   As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.
2. Use in lactation
   Clamentin may be administered during the period of lactation. With the exception of the risk of sensitization associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

Side Effect(s) / Adverse Reaction(s):
Side effects, as with Amoxicillin, are uncommon and mainly of a mild and transitory nature.
Gastrointestinal reactions
Diarrhea, indigestion, nausea, vomiting, candidiasis and antibiotic-associated colitis have been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages.
Hepatic effects
A moderate rise in AST and/or ALT has been noted in patients with beta-lactam class antibiotics, but the significance of these findings is unknown. Hepatitis and cholestatic jaundice have been reported rarely. They may, however, be severe and continue for several months. They are reported as occurring predominantly in adult or elderly patients and slightly more frequently in males. Signs and symptoms may occur during treatment but are more frequently reported after cessation of therapy with a delay of up to six weeks. The hepatic events are usually reversible. However, in extremely rare circumstances, deaths have been reported.
Hypersensitivity reactions
Urticarial and erythematous rashes sometimes occur. Rarely erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have been reported. Treatment should be discontinued if one of these types of rash appears. In common with other β-lactam antibiotics, angioedema, oedema, anaphylaxis, serum sickness-like syndrome and hypersensitivity vasculitis have been reported.
Interstitial nephritis can occur rarely.
Skin and subcutaneous tissue disorders
Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Haematological effects
As with other β-lactams, reversible leucopenia, reversible thrombocytopenia and haemolytic anemia have been reported rarely.
CNS effects
Hyperactivity, dizziness, and headache are rare. Convulsions may occur with impaired renal functions or in those receiving high doses.
Local effects
Thrombophlebitis at the site of injection.

Symptoms and Treatment for Overdosage and Antidote(s):
Cases of overdosage with Amoxicillin-clavulanic acid are usually asymptomatic. If encountered, 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. Clamentin can be removed from the circulation by haemodialysis.

Shelf-life:
2 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 30°C. Protect from light and moisture.

Product description and Packing(s):
A white to off-white powder in vial.

Appearance of reconstituted solution:

1. I.V. injection of WFI, at 25°C, at 10 minutes:	A colorless to pale yellow liquid in vial, and without other foreign matter.
2. I.V. infusion of WFI, at 25°C, at 4 hours:	
3. I.V. infusion of WFI, at 5°C, at 8 hours:	
4. I.V. infusion of 0.9%, w/v NaCl, at 25°C, 4 hours:	

1.2g x 1vial / Case and 1.2g x 10vials / Box

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Manufactured by:
YUNG SHIN PHARMACEUTICAL IND. CO., LTD.
TAICHUNG YOUTH FACTORY III
No. 26 Kung Liu Rd. Youth Industrial District,
Tachia, Taichung, Taiwan, R.O.C.

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