SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

TRICLAV (Co-Amoxiclav for Injection BP 1200mg)

2. COMPOSITION

Each vial contains :

Amoxicillin Sodium BP (Sterile)
Eq to Amoxicillin 1000 mg
Potassium Clavulanic Acid BP (Sterile)
Eq to Clavulanic acid 200 mg

3. PHARMACEUTICAL FORM

Injectable

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Co-Amoxiclav for injection is indicated for the short term treatment of bacterial infections at the following sites:

Upper Respiratory Tract Infections (including ENT): e.g. tonsillitis, sinusitis, otitis media

Lower Respiratory Tract Infections: e.g. acute exacerbations of chronic bronchitis, lobar and broncho-pneumonia

Genito-urinary Tract Infections:e.g.cystitis,urethritis,pyelonephritis,female genital infections

Skin and Soft Tissue Infections: eg. boils, abcesses, cellulites, wound infection

Bone and Joint Infections: e.g. osteomyelitis

Other Infections: e.g. intra-abdominal sepsis

Co-Amoxiclav for injection intravenous is indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract surgery.

4.2 Posology and method of administration; Dosage for treatment of infection

Adults and Children over 12 years: Usually 1200 mg 8 hourly. In more serious infections, increase frequency to 6 hourly intervals.

Children 3 months - 12 years: usually 30mg/kg* Co-Amoxiclav for injection 8 hourly. In more serious infections, increase frequency to 6 hourly intervals.

Children 0-3 months: 30mg/kg* Co-Amoxiclav for injection every 12 hours in Premature infants and full term infants during the perinatal period increasing to 8 hours thereafter.

*Each 30mg Co-Amoxiclav for injection provides 5mg clavulanic acid with 25mg amoxicillin.

Dosage for surgical prophylaxis: the usual dose is 0.2 g. Co-Amoxiclav for injection of anesthesia operations where there is a high risk of infection e.g. colorectal surgery, may require three and up to four, doses of 1.2 g Co-Amoxiclav for injection intravenous in a 24 hour period. These doses are usually given at 0,8,16 (and 24 hrs).This regimen cab be continued for several days if the procedure has significantly increased the risk of infection

Dosage in renal impairment:

Adults: Dosing adjustments are based on the maximum recommended level of Amoxicillin.

	Mild Impairment (creatinine clearance >30mL/min)	Moderate Impairment (creatinine clearance 10-30mL/min)	Severe Impairment (creatinine clearance <10mL/min)
Adults	No change in dosage	1.2g IV stat followed by 600mg IV 12 hourly	1.2g IV stat followed by 600mg IV 24 hourly. Dialysis decreases serum concentrations of Co-Amoxiclav for injection. An additional 600mg IV dose may need to be supplemented at the end of dialysis
Children	No change in dosage	30 mg/kg 12 hourly	30 mg/kg every 24 hours Dialysis decreases serum concentrations of Co-Amoxiclav for injection. An additional 15 mg/kg may need to be supplemented at the end of dialysis, then 30 mg/kg/day

Dosage in hepatic impairment: Dose with caution; monitor hepatic function at regular intervals for both adults and children.

4.3 Contraindications

Hypersensitivity to the constituents, amoxicillin and clavulanic acid. Penicillin hypersensitivity. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. penicillins, cephalosporins, carbapenems, monobactams due to the danger of anaphylactic shock. Consequently a careful history should be taken in regard to allergic reaction before commencing treatment. Co-amoxiclav should not be given to patients with a verified hypersensitivity to any beta-lactam drug.

A previous history of co-amoxiclav or penicillin-associated jaundice/hepatic dysfunction.

Co-amoxiclav may not be used in patients with severe hepatic impairment and in patients in whom hepatic functional impairment has occurred on previous therapy with co-amoxiclav, for example cholestatic jaundice induced by co-amoxiclav or penicillin.

Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukaemia have a higher risk of exanthema and consequently co-amoxiclav injection should not be administered during these diseases to treat concomitant bacterial infections.

4.4 Special warning and special precautions for use

Although severe allergic reactions are more likely in patients who have experienced beta-lactam hypersensitivity, these may occur in the absence of any such history. In such cases treatment should be discontinued immediately and appropriate management instituted.

Co-amoxiclav should be used with caution in patients with allergic diathesis, including asthma, since such patients may have a higher risk of allergic reactions to co-amoxiclav.

Patients with evidence of hepatic dysfunction should be treated with caution. Liver function parameters should be monitored in patients with signs or symptoms of hepatic impairment. Discontinuation of therapy should be considered in case of deterioration of liver function parameters during treatment.

In patients with renal impairment, excretion of co-amoxiclav will be delayed and depending on the degree of the impairment, it may be necessary to reduce the total daily dosage

In long term use (more than 10-14 days), regular monitoring of renal and hepatic function is recommended.

Prolonged use of co-amoxiclav, or other broadspectrum antibiotics, may lead to superinfections due to an overgrowth of non-susceptible organisms and yeasts.

In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered, in which case therapy should be discontinued.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

4.5 Interaction with other medicaments and other forms of interaction.

Other bacterial agents: There is a possibility that the antibacterial action of amoxicillin could be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Probenecid : By inhibiting the renal elimination of amoxicillin (but not clavulanic acid) the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Allopurinol : Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions.

Digoxin: An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin.

Co-amoxiclav / disulfiram : Co-amoxiclav should not be used concurrently with disulfiram.

Methotrexate : Concomitant administration with methotrexate may lead to an increase in toxicity of methotrexate.

Anticoagulants: Concomitant administration of amoxicillin and coumarin anticoagulants, such as warfarin, may increase the incidence of bleeding.

Oral hormonal contraceptives: Administration of amoxicillin can transiently decrease the plasma level of oestrogens and progesterone and may reduce the efficacy of oral contraceptives. Patients should be advised to use supplemental non-hormonal contraceptive measures.

Other forms of interaction: Amoxicillin may produce false positive results in glucose determination tests and tests for urobilinogen performed with nonenzymatic methods. Likewise the urobilinogen test can be affected.

Amoxicillin may decrease the amount of urinary estriol in pregnant women. Diarrhoea may decrease the absorption of other drugs and consequently have a negative influence on their effectivity.

Forced diuresis will lead to an increased elimination of amoxicillin resulting in decreased serum concentrations.

4.6 Pregnancy and Lactation

Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. There is limited experience of the use of co-amoxiclav in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Co-amoxiclav 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.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8. Undesirable effects

The most commonly reported adverse drug reactions are hypersensitivity reactions:

Common (≥ 1% but < 10%)

Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5-11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Other possible side effects:

Blood disorders:

There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time and prolongation of prothrombin time. However, these changes were reversible on discontinuation of therapy.

Gastrointestinal disorders:

Common (≥ 1% but < 10%):

Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking amoxicillin during meals or with some food. If severe and persistent diarrhoea occurs, the rare possibility of pseudomembraneous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

CNS disorders:

CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Other undesirable effects

Prolonged and repeated use of the preparation can result in superinfections and colonisation with resistant organisms or yeasts such as oral and vaginal candidiasis.

4.9 Overdose and Treatment

Symptoms of overdosage

In the event of overdosage, gastrointestinal symptoms, such as nausea, vomiting and diarrhoea and disturbances of the fluid and electrolyte balance are possible. Also, convulsions may exist.

Management of overdosage

There is no specific antidote for overdose. Treatment consists of haemodialysis and symptomatic measures paying particular attention to the water and electrolyte balance, especially if there are any gastro-intestinal symptoms. Administration of medicinal charcoal and gastric lavage are useful only in cases of very high overdose (> 250mg/kg). In case of severe renal insufficiency, Co-amoxiclav can be eliminated from the circulation via haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Resistance to many antibotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen.The clavulanate in Co-Amoxiclav for injection anticipates this defense mechanism by blocking the-lactamase enzymes.thus rendering the organisms sensitive to amoxicillin's rapid bactericidal effects at concentrations readily attainable in the body.

Clavulanate by itself has little anti-bacterial activity; however, in association with amoxicillin as Co-Amoxiclav for injection it produces an antibiotic agent of broad spectrum with wide application in hospital in and general pracice.

CO-AMOXICLAV FOR INJECTION is bactericidal to a wide range of organisms including:

- **Gram-positive aerobes:**

  Bacillus anthracis*,Corynebacterium species,Enterococcus faecalis *,Enterococcus faecium * Listeria monocytogenes,Nocardia asteroides,Staphylococcus aureus*,Coagulase negative staphylococci* (including Staphylococcus epidermidis*),Streptococcus agalactiae,Streptococcus pneumoniae,Streptococcus pyogenes,Streptococcus species,Streptococcus viridans

- **Gram-positive anaerobes:**

  Clostridium species, Peptococcus species,Peptostreptococcus species

- **Gram-negative aerobes:**

  Bordetella pertussis,Brucella species,Escherichia coli*,Gardnerella vaginalis,Haemophilus influenzae*,Helicobacter pylori,Klebsiella species*,Legionella species,Moraxella catarrhalis* (Branhamella catarrhalis),Neisseria gonorrhoeae*,Neisseria meningitidis *,Pasteurella multocida,Proteus mirabilis*,Proteus vulgaris*,Salmonella species*,Shigella species*,Vibrio cholerae,Yersinia enterocolitica*

- **Gram-negative anaerobes:**

  *Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to Amoxicillin alone.

Infection caused by amoxicillin susceptible organisms are amenable to CO-AMOXICLAV FOR INJECTION treatment due to its amoxicillin content.ixed infection caused by amoxicillin

susceptible to organisms in conjugation with CO-AMOXICLAV FOR INJECTION susceptible-lactamase producing organisms may therefore be treated with CO-AMOXICLAV FOR INJECTION.

5.2 Pharmacokinetic Properties

The pharmacokinetics of the two cpmponents of CO-AMOXICLAV FOR INJECTION are closely matched. Both Clavulanate and Amoxicillin have low level of serum binding about 70 % remain free in the serum.Doubling the doses of CO-AMOXICLAV FOR INJECTION approximately double the serum level achieved.

5.3 Preclinical Safety Data

a) Acute toxicity

Investigations of the acute toxicity (LD_{50}) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD_{50} of clavulanic acid (potassium salt) is determined by the potassium content.

Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

b) Chronic toxicity / subchronic toxicity

Extensive studies of the chronic toxicity have been carried out based on international standards. Solely after high doses (corresponding to 20- to 50- fold the maximal human dose) were mild haematological and blood-chemical changes observed which regressed completely following discontinuation of the therapy.

c) Mutagenic and tumorigenic potential

In-vitro and in-vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

d) Reproductive toxicity

After treatment of various infections in pregnant women (approximately 560 pregnancies) with Co-amoxiclav no increased occurrence of malformations was observed. Amoxicillin and clavulanic acid diffuse through the placenta and are excreted into breast milk (probable elimination of clavulanic acid into breast milk).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:- None

6.2 Incompatibilities

None stated.

6.3 Shelf Life

36 months from the date of manufacturing.

6.4 Special Precautions for Storage

Protect from light. Store at the temperature below 30ºC.

6.5 Nature and Contents of container

(1000+200) mg of Co – Amoxiclav for Injection BP in glass vial with rubber stopper and aluminium flip off seal. Each vial is placed in unit carton along with Sterile WFI & package insert.

6.6 Instructions for user handling

Unused medicine and all waste materials should be destroyed according to standard procedures.

6.7 Marketing Authorisation Holder
ALCHEMY MEDICINE PVT. LTD.

7. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
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8. DATE OF (PARTIAL) REVISION OF THE TEXT
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