MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Co-Amoxiclav for Injection BP 1.2 gm **(**AMOVIN – 1.2 gm)

1.1 (Invented) name of the medicinal product:

Generic name/INN name:

Co-Amoxiclav for Injection BP 1.2 gm

1.2 Strength:

Each vial contains:

Potassium Clavulanate BP

Eq. to. Clavulanic acid …….. 200 mg

Amoxicillin Sodium BP

Eq. to. Amoxicillin ……. 1000 mg

1.3 Pharmaceutical form:

Powder for Injection

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2. Qualitative and Quantitative Composition:

Sr. No.	Ingredients	Spec.	Label Claim	Qty./ Tab mg.	% w/w	Function
1.	Sterile mixture of Clavulanate Potassium with Amoxicillin Sodium (5:1) *	BP	1.2 gm	1.2 gm	100.0 %	Active Pharmaceutical Ingredients

Note:
* Quantity calculated on based of Assay and Water Content of sterile mixture.

3. Pharmaceutical form:

Dosage Form: Powder for Injection

Visual & Physical characteristics of the product:

A white coloured free flowing powder filled in an intactly sealed clear glass vials.

4. Clinical particulars:

4.1 Therapeutic indications:

This product is indicated for the short-term treatment of the following infections caused by sensitive bacteria:

• Upper respiratory tract infection (including ear, nose and throat): such as recurrent tonsillitis, sinusitis, otitis media.

• Lower respiratory tract infection: such as acute exacerbations of chronic bronchitis, lobar pneumonia and bronchopneumonia.

• Urogenital tract infection: such as cystitis, urethritis, pyelonephritis.

• Skin and soft tissue infection: such as furuncle, abscess, cellulitis, traumatic infection.

• Bone and joint infection: such as osteomyelitis.

• Other infections: such as abdominal infection and so on.

This product can also be used to prevent major surgical infection, such as: gastrointestinal, pelvic, head, neck, heart, kidney, joint transplantation and biliary tract surgery.

4.2 Posology and method of administration:

Dosages for infection treatment

For adults and children over 12 years old	Normal dosage: 1.2g every 8 hours; Severely infected person: it can be increased to1.2g every 6 hours.
For children aged 3	Normal dosage: 30mg*/kg of body weight every8 hours; Severely

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months-12 years old	infected person: it can be increased to30mg*/kg of body weight every 6 hours.
For children aged 0-3 months	Perinatal preterm infants and full-term new-borns, 30mg*/kg of body weight every 12hours; then increased to 30mg*/kg of body weight every 8 hours.

*Per 30mg of this product contains 25mg of Amoxicillin and 5mg of Clavulanate

Dosages for adults to prevent surgical infection

It is usually administrated intravenously during anesthesia induction. For surgery with high risk of infection, such as colon surgery patients, this product can be administrated 3 to 4 times within 24hours, each time 1.2g, at 0, 8, 16 and 24 hours. If the risk of infection increases during the surgery, it can be administrated for several days continuously as per this regimen. If there are obvious signs of infection during the operation, intravenous administration of this product or oral administration of amoxicillin and potassium clavulanate tablets should be continued for a course after surgery.

Dosages for patients with renal insufficiency

Adults:

Mild damage (creatinine clearance rate > 30 ml/min)	Moderate damage (creatinine clearance rate is 10~30 ml/min)	Severe damage (creatinine clearance rate <10ml/min)
No change in the dosage	Administrate 1.2g of this product at the beginning, and then administrate 0.6g every 12 hours.	Administrate 1.2g of this product at the beginning, and then administrate 0.6g every 24hours. Dialysis method can reduce the concentration of this product in the blood, and 0.6g of this product should be administrated during or after dialysis.

Children: reduce the dosage in the same manner.

Dosages for patients with hypohepatia: administrate with caution and test liver function regularly. Per 1.2g of this product contains about 1.0mmol potassium and 3.1mmol sodium.

Administration: Intravenous injection or intravenous drip, and not suitable for intramuscular injection. Reconstitute per 300mg of this product with 5ml of WFI. Namely reconstitute 0.6g of this

product with 10ml of WFI, and 1.2g of this product with 20ml of WFI. A temporary pink color may appear during the reconstitution, and the resulting injection is usually almost white or yellowish.

Intravenous injection: The stability of injection is related to its concentration. The prepared injection should be used immediately within 20 minutes, and injected slowly for 3~4 minutes. This product can also be injected into the vein directly or via the ductus venosus.

Intravenous drip: The injection of this product can be prepared with WFI or normal saline (0.9%w/v). Then, don't procrastinate*, dilute the injection of 0.6g of this product into 50ml of drip solution, or dilute the injection of 1.2g of this product into 100ml of drip solution (for example: use a pouch or a graduated test tube). The prepared infusion should be dripped for 30~40 minutes, within 3 hours.

In addition, other injectable solutions can be used to prepare the injection of this product. Prepare the injection with appropriate concentration using injectable solutions below, and stored at 5℃ or room temperature (25℃), the prepared injection should be dripped within the time indicated in the following table.

Intravenous infusion solution	**Stable time at 25℃**
WFI	3 hours
0.9% (w/v) sodium chloride intravenous infusion solution	3 hours
Compound sodium chloride intravenous infusion solution (Ringer injection)	2 hours
Compound sodium lactate intravenous infusion solution (Ringer-lactic acid solution. Hartmann's solution)	2 hours
Potassium chloride and sodium chloride intravenous infusion solution	2 hours

Don't freeze the prepared injection. This product is relatively unstable in drip solutions containing glucose, glucan or bicarbonate, so the prepared injection shouldn't be added to such injectable solutions, but can be injected into the still gout within 3~4 minutes. Add the prepared injection to the pre-cooled drip bag, and can be stored stably for 8 hours at 5℃. The injection should be used immediately when its temperature reaches room temperature.

Intravenous fluid	**Stable time at 5℃**
WFI	8 hours
Sodium chloride intravenous infusion solution (0.9% w/v)	8 hours

*The solution should be added to the full drip immediately after preparation.

Remaining medicine liquid should be discarded.

Treatment can begin with parenteral administration, and then continue the treatment with oral preparation. The treatment period of this product shouldn't be more than 14 days without re-examination.

4.3 Contraindications:

• This product is contraindicated in patients with positive reaction of penicillins skin test, with a history of allergic reactions to this product and other penicillins and patients with infectious mononucleosis.

• Previous history of amoxicillin and clavulanate-associated cholestatic jaundice or hepatic dysfunction.

4.4 Special warnings and precautions for use:

• The product should be used with caution in patients allergic to cephalosporin's and having the history of asthma, allergic rhinitis, urticaria and other allergic diseases.

• The product has cross-anaphylaxis with other penicillins and cephalosporin's. If such cases occur, administration of this product should be discontinued immediately and take appropriate measures.

• The product has cross-resistance with ampicillin and other penicillins and cephalosporin's.

• The product should be administered immediately after reconstituted. The remaining medicine liquid should be discarded and not be reused. The prepared solution of the product cannot be cryopreservation.

• The stability of the product is reduced in the solution containing glucose, glucan or acidic carbonate, so the product cannot be mixed with the solution containing the above-mentioned substances.

• The solution of the product cannot be mixed in vitro with blood products, the solution containing protein (such as protein hydrolysate) and vein lipid emulsifying agent.

• The product cannot be mixed in vitro with aminoglycoside antibiotic, since it can cause the activity loss of the latter.

• The product should be used with caution when glomerular filtration rate is less than 30ml/min. The patients with renal dysfunction should be administered by adjusting dose or administration interval according to glomerular filtration rate; haemodialysis may affect the plasma concentration of amoxicillin, so at the end of haemodialysis, an additional dose of this product should be administered.

• Advise patients that when taking large dose of amoxicillin, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

• The product should be used with caution in patients with hepatic insufficiency.

• The patients in long term use or at high doses should be monitored the function of liver, kidney and hematopoietic system and test serum potassium or sodium.

• The dosage of oral anticoagulant should be adjusted when combined with Warfarin to keep the needed anticoagulation level.

• This product should be taken according to specification strictly as is a time dependent antibiotic, the interval between multiple doses should not be less than 6 hours.

• This product should be administrated intravenously or by intravenous drip, and it is not suitable for intramuscular injection.

• Continuous medication in some cases leading to overgrowth of non-sensitive bacteria, pseudomembranous enteritis has been reported. If persistent and severe diarrhoea or abdominal colic occurred, administration of this product should be discontinued immediately and further checks instituted.

• In order to ensure the effectiveness of treatment and to avoid bacterial resistance, medication should be used according to the doctor's advice to avoid omission or early withdrawal.

• If the patient is required to receive a large dose of this product, for patients on sodium-restricted diets, the sodium content of the product should be included in the total sodium intake.

• For the patients suspected to suffer from gonorrhoea companied with syphilis injury, before using this product, dark-field microscopy should be performed and in at least four months, the above-mentioned patients should be given serum test once per month.

• Disturbance of test index in the laboratory:

- The test for urinary glucose performed with copper sulphate method appears false positive results, but the results in test performed with glucose enzymes method cannot be affected. When using this product, urine glucose test based on glucose oxidase reaction is recommended;

- It can affect the serum alanine aminotransferase or aspartate aminotransferase determination value.

• No adverse effects have been found on drivers and mechanicians.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended to use this product in combination with probenecid, because probenecid can reduce renal tubule secretion of amoxicillin, and the combination can lead to an increase in

amoxicillin plasma concentration and a prolongation of half-life, but does not affect clavulanic acid plasma concentration.

Although there is no data on the use of this product in combination with allopurinol, the combination of amoxicillin and allopurinol may increase the likelihood of allergic skin reactions.

As with other antibiotics, this product may affect the intestinal flora, resulting in reduced estrogen reabsorption and reducing the effectiveness of combined oral contraceptives.

The literature reports rare cases in which a course of amoxicillin was used while maintaining acenocoumarin or warfarin, the international normalized ratio (INR) increases. If concomitant medications are required, carefully monitor prothrombin (PT) or INR when amoxicillin is added or withdrawn.

Pre-administration concentrations of the active metabolite mycophenolic acid have been reported to decrease by approximately 50% in patients receiving mycophenolate after beginning oral administration of amoxicillin and clavulanic acid. Changes in levels before administration may not accurately reflect changes in total MPA exposure.

4.6 Fertility, Pregnancy and lactation:

Pregnancy: Reproductive toxicity tests in animals (rats and mice) showed no teratogenic effects of oral or parenteral administration of this product. In a separate study of premature rupture of membranes (pPROM), prophylactic use of amoxicillin sodium and potassium clavulanate has been reported to increase the risk of necrotizing enterocolitis in newborns. Use of this product in pregnant women is limited and, as with all medications, it should be avoided unless deemed necessary by a physician, especially during the first trimester of pregnancy.

Lactation: You can use this product during lactation. Trace amounts of this product secreted into the milk, in addition to the risk of allergy, no harm to lactating infants.

Fertility: Not known.

4.7 Effects on ability to drive and use machines:

No adverse effects have been found on drivers and mechanicians.

4.8 Undesirable effects:

Lesions of skin and its appendages: Rashes, pruritus, hives, skin flush, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Exfoliative dermatitis (erythroderma), acute generalized exanthematous pustulosis.

Gastrointestinal impairment: Nausea, vomiting, indigestion, abdominal distension, diarrhea, gastritis, stomatitis, glossitis, black "hairy" tongue, pseudomembranous colitis and hemorrhagic colitis.

Immune function disorders and infections: Drug induced fever, hypersensitivity vasculitis, angioedema, mucocutaneous candidiasis, superinfection, serum sickness-like reactions (urticaria accompanied by arthritis, arthralgia, myalgia, and fever), asthma, severe anaphylaxis and anaphylactic shock.

Nervous system impairment: Headache, dizziness, vertigo, insomnia, agitation, anxiety, dysphoria, behavioral changes, confusion and convulsions.

Injection part impairment: Injection part pain, phlebitis or thrombophlebitis.

Hematologic system impairment: Leukopenia (including neutropenia) and thrombocytopenia, thrombocytopenic purpura, eosinophilia, thrombocytosis, prolongation of prothrombin time, agranulocytosis, and hemolytic anemia.

Genitourinary impairment: Hematuria, crystalluria, interstitial nephritis, acute renal injury (including creatinine increase and acute renal failure).

Hepatobiliary impairment: Transaminase elevation, hepatitis and cholestatic jaundice.

Other impairments: Palpitation, cyanosis, dyspnea, oppression in chest and chills.

4.9 Overdose:

Patients with overdose are usually asymptomatic. Once they occur, the main manifestations are gastrointestinal symptoms, water and electrolyte disturbances. Symptomatic treatment with water and electrolyte can be used to maintain the balance of water and electrolyte. The product in the blood can be cleared by dialysis. Amoxicillin crystalluria has been reported to cause renal failure in some patients (see special warnings and precautions for use). High doses of intravenous administration have caused amoxicillin to precipitate in the vesical ureter. Regular check of smoothness should be performed regularly.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors

ATC code: J01CR02

Amoxicillin is a semi-synthetic antibiotic with in vitro bactericidal activity against gram-positive and gram-negative bacteria. However, amoxicillin is easily degraded by β-lactamase, so its

antibacterial activity profile does not include microorganisms capable of producing these enzymes. Clavulanic acid is a β-lactam structurally related to penicillin and has the ability to cause β-lactamase inactivation common in some penicillin and cephalosporin-resistant microorganisms. In particular, it has good activity on the clinically important plasmid-mediated β-lactamases, which often cause the transfer of drug resistance. The combination of amoxicillin and clavulanic acid prevents the degradation of amoxicillin by certain β-lactamases, thus expanding the antibacterial profile of amoxicillin and making it active against many bacteria that are normally resistant to amoxicillin. Amoxicillin/clavulanic acid has been shown to be active against most strains of the following bacteria.

Gram-positive bacteria Staphylococcus Aureus Gram-negative bacteria Enterobacter Escherichia coli Haemophilus influenza Klebsiella Moraxella catarrhal the following in vitro data have been obtained, but its clinical significance is unclear. The minimum inhibitory concentration (MIC) in vitro was less than or equal to the amoxicillin/clavulanic acid sensitivity threshold for at least 90% of the following bacteria. However, the efficacy of amoxicillin/clavulanic acid against clinical infections caused by these bacteria has not been established in sufficient and well-controlled clinical trials.

Gram-positive bacteria: Enterococcus faecalis Staphylococcus epidermidis Staphylococcus saprophyticus Streptococcus Pneumonia Streptococcus Pyogenes Streptococcus vermicularis group.

Gram-negative bacteria: Eikenella corrodens Proteus Mirabilis Anaerobic bacteria Bacteroides, including Bacteroides fragilis Clostridium Digestive Streptococcus.

5.2 Pharmacokinetic properties:

The pharmacokinetic parameters of amoxicillin and clavulanic acid are very similar. The serum protein binding of amoxicillin and clavulanic acid is very low and about 70% is present in the serum in free form. The dose of this product is doubled, and the plasma concentration is also doubled.

5.3. Preclinical safety data:

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Not applicable

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6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 Months

6.4 Special precautions for storage:

Store in a cool & dry place, below 25°C. Protect from light.

6.5 Nature and contents of container:

Primary packing: 20 ml clear glass vial USP Type – I.

Secondary packing: Such 10 vials are packed in monocarton along with package insert.

6.6 Special precautions for disposal:

This medicinal product does not require any special storage conditions.

7. Applicant:

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