SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Amoxicillin sodium and potassium clavulanate for injection 1.2g

2. Qualitative and quantitative composition

Each vial contains about 1.063g of Amoxicillin sodium, equivalent to 1.0g of Amoxicillin and 0.238g of Potassium clavulanate, equivalent to 0.2g of Clavulanate.

For accompanying reconstitution diluent:

Each ampoule contains 10 mL of sterile water for injection.

3. Pharmaceutical form

Powder for injection.

4. Clinical particulars

4.1 Therapeutic indications

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

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

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

(3) Urogenital tract infection: such as cystitis, urethritis, pyelonephritis.

(4) Skin and soft tissue infection: such as furuncle, abscess, cellulitis, traumatic infection.

(5) Bone and joint infection: such as osteomyelitis.

(6) 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 Administration and dosages

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 to 1.2g every 6 hours.
For children aged 3 months-12 years old	Normal dosage: 30mg*/kg of body weight every 8 hours; Severely infected person: it can be increased to 30mg*/kg of body weight every 6 hours.
For children aged 0-3 months	Perinatal preterm infants and full-term newborns, 30mg*/kg of body weight every 12 hours; 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 24 hours, 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 >30ml/min)	Moderate damage (creatinine clearance rate is 10~30ml/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 24 hours. 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 stilligout 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 reexamination.

4.3 Contraindications

1. 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.
2. Previous history of amoxicillin and clavulanate-associated cholestatic jaundice or hepatic dysfunction.

4.4 Special warnings and precautions for use

(1) The product should be used with caution in patients allergic to cephalosporins and having the history of asthma, allergic rhinitis, urticaria and other allergic diseases.

(2) The product has cross-anaphylaxis with other penicillins and cephalosporins. If such cases occur, administration of this product should be discontinued immediately and take appropriate measures.

(3) The product has cross-resistance with ampicillin and other penicillins and cephalosporins.

(4) 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 can not be cryopreservation.

(5) The stability of the product is reduced in the solution containing glucose, glucan or acidic carbonate, so the product can not be mixed with the solution containing the above mentioned substances.

(6) The solution of the product can not be mixed in vitro with blood products, the solution containing protein (such as protein hydrolysate) and vein lipide emulsifying agent.

(7) The product can not be mixed in vitro with aminoglycoside antibiotic, since it can cause the activity loss of the latter.

(8) 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; hemodialysis may affect the plasma concentration of amoxicillin, so at the end of hemodialysis, an additional dose of this product should be administered.

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

(10) The product should be used with caution in patients with hepatic insufficiency.

(11) 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.

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

(13) 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.

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

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

(16) 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.

(17) 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.

(18) For the patients suspected to suffer from gonorrhea 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.

(19) Disturbance of test index in the laboratory:

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

(b) It can affect the serum alanine aminotransferase or aspartate aminotransferase determination value.

(20) No adverse effects have been found on drivers and mechanicians.

4.5 Interaction with other medicinal products

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 acetocoumarin 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.

Preadministration 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 Pregnancy and lactation

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.

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.

4.7 Effects on ability to drive and use machines

No adverse effects have been found on drivers and mechanicians.

4.8 Undesirable effects

(1) 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.

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

(3) 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.

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

(5) Injection part impairment: Injection part pain, phlebitis or thrombophlebitis.

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

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

(8) Hepatobiliary impairment: Transaminase elevation, hepatitis and cholestatic jaundice.

(9) 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 (refer to **D.4 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 Pharmacology and toxicology

Pharmacology

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 in vitro and in clinical infections.

Gram-positive bacteria Staphylococcus aureus **Gram-negative bacteria** Enterobacter Escherichia coli Haemophilus influenzae 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

Drug sensitivity test

When possible, the clinical microbiology laboratory should provide clinicians with periodic reports on the drug susceptibility profile of hospital-acquired and community-acquired pathogens. This report should be a cumulative report of the results of in vitro drug susceptibility tests for antibiotics used in the local hospital and practice area. These reports should help doctors choose antibiotics for treatment.

Dilution method

The minimum inhibitory concentration (MIC) of antibiotics can be determined by quantitative methods, and the MIC can be used to evaluate the sensitivity of bacteria to antibiotics. Standard test methods (broth or AGAR) should be used to determine MICs, and the measured MICs values can be interpreted according to the criteria in the table below.

Diffusion method

The quantitative method of measuring the diameter of the inhibition zone can also be used to

reproducibly estimate the susceptibility of bacteria to antimicrobial chemicals. A standardized method should be used to determine the size of the inhibition zone. Bacterial susceptibility to amoxicillin/clavulanic acid was tested using a disk containing 30μg of amoxicillin/clavulanic acid (20μg of amoxicillin+10μg of clavulanic acid). The following table provides the breakpoint criteria for the disk diffusion method.

Amoxicillin/clavulanic acid susceptibility criteria

Pathogenic bacteria	Dilution method (MIC, μg/ml)			Diffusion method (Inhibition zone diameter, mm)		
	Sensitive (S)	Intermediate (I)	Resistant (R)	Sensitive (S)	Intermediate (I)	Resistant (R)
Enteric bacilli	8/4	16/8	32/16	≥18	14-17	≤13
Haemophilus influenza and Staphylococcus aureus	4/2	--	8/4	≥20	--	≤19

Quality control

A standardized approach to susceptibility testing requires the use of laboratory quality-control measures to monitor and ensure the accuracy and precision of the articles and reagents used in the test and the correct practices of test operators. Standard amoxicillin/clavulanic acid powders should obtain the following MIC ranges listed in the table below. The diffusion method using a 30μg of amoxicillin/clavulanic acid (20μg of amoxicillin+10μg of clavulanic acid) disk should meet the criteria listed in the table below.

Acceptable quality control range of Amoxicillin/clavulanic acid

Quality control strain	Dilution method MIC (μg/ml)	Diffusion method (Inhibition zone diameter, mm)
Escherichia Coli ATCC* 25922	2/1 – 8/4	18-24
Escherichia Coli ATCC 35218	4/2 – 16/8	17-22
Haemophilus influenza ATCC 49247	2/1 –16/8	15-23
Staphylococcus aureus ATCC 29213	0.12/0.06 – 0.5/0.25	--
Staphylococcus aureus ATCC 29523	--	28-36

*ATCC=American Type Culture Collection

Toxicology

Genotoxicity

Amoxicillin/clavulanate (4:1) has not been shown to be mutagenic in either the Ames test or the yeast gene transformation test. The lymphoma test in mice was weakly positive, but in this test, the trend toward increased mutation frequency coincided with decreased cell survival. The mouse

micronucleus test and the mouse dominant lethal test were negative. The Ames test and mouse micronucleus test performed with clavulanic acid alone were negative.

Reproductive toxicity

When rats were orally administrated amoxicillin/clavulanic acid (2:1) 1200mg/kg/day, calculated by body surface area, approximately four times the maximum recommended oral dose for adults for amoxicillin (875mg/12 h) and nine times for clavulanic acid (125mg/8 h), no effect on fertility or reproductive behavior was observed.

When pregnant rats and mice were orally administrated amoxicillin/clavulanic acid (2:1) 1200mg/kg/day, calculated by body surface area, the amoxicillin dosage of rats and mice was approximately four times and two times the maximum recommended oral dose for adults respectively and the clavulanic acid dosage was approximately nine times and four times, no adverse effect on the fetus was observed.

Carcinogenicity

Carcinogenicity studies have not been performed.

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

There are no data available.

6. Pharmaceutical particulars

6.1 List of excipients

There are no excipients added in this product.

Accompanying reconstitution diluent: Sterile

water for injection 10 mL

6.2 Incompatibilities

This product only contains API, without any excipient. The API is filled in glass vials, and the compatibility of API and vials are good under recommended storage conditions. The stability results refer to 3.2.P.8.3 of Module 3 Quality, which demonstrates that the API is stable in the commercial package under recommended storage conditions.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Airtight, preserve from light, store in a dry place not exceeding 30℃.

6.5 Commercial presentation

Amoxicillin sodium and potassium clavulanate for injection 1.2g: 20-mL type-A moulded vials, one vial accompanies two ampoules of 10mL sterile water for injection/box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed in accordance with local requirements.

7. Marketing authorization holder

Shandong Lukang Pharmaceutical Co., Ltd.

Address: 88 Deyuan Road, High-Tech Zone, Jining, Shandong, P.R. China

8. Manufacturing site and address

Shandong Lukang Pharmaceutical Co., Ltd.

Address: 88 Deyuan Road, High-Tech Zone, Jining, Shandong, P.R. China

9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text

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