SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Ceftriaxone Sodium for Injection 1.0 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial Ceftriaxone contains 1.196 g of ceftriaxone sodium, equivalent to 1.0 g of ceftriaxone.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Respiratory infection (especially pneumonia), ENT infection (such as acute otitis media), urinary system infection, sepsis, meningitis (such as early and late stage of disseminated Lyme disease), bone and joint infections, skin soft-tissue infection, intra-abdominal infection (peritonitis, biliary and gastrointestinal infections), reproductive tract infection including gonorrhea caused by pathogenic bacteria sensitive to the product, also for preoperative infection prevention.

4.2 Posology and method of administration

[Posology and method of administration]

Adults, children aged over 12 years and children weighed more than 50 kg should all be given adult dose, normally 1 - 2 g, once daily; for critical patients or patients with infection induced by moderately sensitive bacteria, the dose can be increased to 4 g, once daily.

For neonatus, infants and children aged below 12 years old, the following doses once daily are recommended: daily dose for neonatus (under 14 days) is 20-50 mg/kg by body weight, no more than 50 mg/kg, no need to distinguish premature baby and full-term baby. The daily dose for infants and children (15 days to 12 years old) is 20 - 80 mg/kg by body weight.

Course of treatment The course of treatment depends on course of disease, normally for 4 - 14 days, and can be extended appropriately in the case of severe complex infection. The same as general antibiotic therapy, the product should be continued for 48 - 72 h at least after fever abated or evidence of bacterial clearance is obtained.

Instruction for specific medication Meningitis: For infants and children with bacterial meningitis, initial therapeutic dose is 100 mg/kg by body weight (no more than 4 g), once daily. Once pathogenic bacteria and drug susceptibility result are confirmed, the dose can be reduced as appropriate. Acute otitis media: For children and adults, 50 mg/kg by body weight and the maximum dose is no more than 1 g. Gonorrhoea: Recommended usage for treatment of gonorrhoea (penicillinase-producing and penicillinase-absent strains) is single-dose intramuscular injection of 250 mg. Preoperative prophylaxis: Prophylaxis for infection following contaminated or uncontaminated surgery, depending on level of infection risk, it is recommended to

inject single-dose of 1 - 2 g of the product 30 - 90 min prior to surgery. It has been proved that the product used individually or combined with 5-nitromidazole (such as ornidazole) (administrated separately) is effective in patients undergoing colonic and rectal surgery. Hepatic and renal insufficiency: For patients with renal insufficiency, there is no need to reduce the drug dosage if hepatic function had no impairment. For patients with severe renal failure (creatinine clearance < 10 ml /min), daily dosage of the product should be no more than 2 g. For patients with impaired liver function, there is no need to reduce the dose if renal function is in good condition. Plasma concentration of the product should be monitored on a regular basis for patients with severe hepatic and renal dysfunction. For patients on dialysis therapy, there is no need to give additional dose after dialysis since the drug clearance in these patients may decrease and plasma concentration should be monitored to determine whether dose adjustment is required.

Method of administration

Intramuscular injection: 1.0 g of the product is dissolved in 3.5 ml of 1% Lidocaine hydrochloride for intramuscular injection. It is preferred to inject at relatively larger muscle site and it is not recommended to inject more than 1 g in muscle at the same site. Lidocaine solution must not be given by intravenous injection.

Intravenous injection: 1.0 g of the product is dissolved in 10 ml sterilized water for injection for intravenous injection and injection time should be no less than 2 - 4 min.

Intravenous infusion: 2 g of the product is dissolved in 4 ml 0.9% sodium chloride solution or 5% glucose injection and diluted with the same solvent to 100 - 250 ml for intravenous drip. In case of intravenous dose over 50 mg/kg by body weight, the infusion time should be at least 30 min.

4.3 Contraindications

The product is contraindicated in patients allergic to cephalosporin.

4.4 Special warnings and special precautions for use

4.4.1. The allergic history should be consulted in details prior to medication. Any patient with allergic constitution should use the product with caution. Patients allergic to penicillin may experience cross-allergic reaction to the product and should use it with caution.

4.4.2. The same as other cephalosporin, although the complete medical history of patient has been acquired, possibility of allergic shock cannot be excluded. Once allergic shock occurs, epinephrine should be administrated immediately or other emergency measures should be taken immediately.

4.4.3. Almost all antibiotics including cefatriaxone have been reported to be associated with pseudomembranous enteritis; therefore it is very important to consider this diagnosis for patients with diarrhoea after receiving antibiotics. After confirming the diagnosis, discontinue the medication for mild cases and for moderate to severe cases, fluid, electrolytes and proteins should be supplemented and effective antibacterial should be given. Patients with history of gastrointestinal disorder should use the product with caution.

4.4.4. The product may lead to prothrombin time prolonged in patients with vitamin K deficiency. Prothrombin time should be monitored and vitamin K can be supplemented if necessary.

4.4.5. Gallbladder sonogram disorder has been reported during medication of the product due to shadow caused by deposition of ceftriaxone calcium salt, which may be misdiagnosed as gallbladder calculus. The shadow will disappear with the end of treatment or discontinuation of medication. In rare cases, the foregoing examination will be accompanied with symptoms and gallbladder disease may even occur in some cases. Therefore, once foregoing symptom occurs, the product should be discontinued and conservative non-surgical treatment is recommended.

4.4.6. Studies have shown that cefatriaxone will replace bilirubin from plasma albumin as other cephalosporin. When the product is used for a long time, hemogram should be monitored regularly.

4.4.7. Influence on ability of driving vehicles and operating machinery: There is no adverse effect on driving vehicles or operating machinery as indicated in study data.

4.4.8. Influence on diagnostic test: When the product is used for treatment, Coombs' test may present false positive result in very few cases. The same as other antibiotics, the product may also cause false positive result in blood galactose test. Therefore urine sugar level should be determined by enzymic method during use of the product.

4.4.9. Immiscibility: The product cannot be mixed in calcium-containing solution such as Hartman's solution and Ringer's solution. According to literature report, the product is immiscible with triamterene, vancomycin, fluconazole and aminoglycoside antibiotics. They cannot be mixed. The product has many incompatibilities and therefore should be given separately.

4.4.10. Stability: The product is a β-lactamase antibiotic which should be prepared before use.

4.5. Interaction with other FPPs and other forms of interaction

1. So far renal insufficiency caused by large dose of the product and diuretic (e.g. furosemide) has not been identified. It is not found that the product increases nephrotoxicity of aminoglycoside antibiotics.

2. No abstinence-like side effect is found in patients who receive the product after drinking, however, alcohol and alcoholic beverages should still be avoided when using the product.

3. Cefatriaxone does not contain N-thiotetrazole which is associated with hemorrhage symptom in some other cephalosporin antibiotics.

4. Clearance of the product is not impacted by probenecid.

5. It is found in vitro test that chloramphenicol combined with cefatriaxone may cause antagonistic effect. The intravenous infusion of cephalosporins may turn turbid when erythromycin, tetracycline, amphotericin B, vasoactive drug (metaraminol, norepinephrine, etc.) phenytoin sodium, chlorpromazine, isopropanol, vitamin B

family or vitamin C is added. The product has many incompatibilities and therefore should be given separately.

4.6. Pregnancy and lactation

No embryotoxicity and teratogenicity are detected in reproductive toxicity test with 20 folds of human dose in mice and rats. Fully well-controlled clinical trial has not yet been carried out in pregnant women. Results of animal test cannot fully reflect human toxicity, therefore pregnant and lactating women should use the product when absolute necessary.

4.7. Effects on ability to drive and use machines

There is no adverse effect on driving vehicles or operating machinery as indicated in study data.

4.8. Undesirable effects

The product is well-tolerated and has few adverse reactions which occurs at about 5 - 7%, manifested as mild allergic reaction including rash, pruritus, urticaria, edema, erythema multiforme, fever and bronchial spasm; gastrointestinal reactions including nausea, vomiting, abdominal pain, abdominal distension, soft stool, diarrhoea, glottitis, gastritis, colonitis, parageusia and jaundice; neurologic reactions including headache and vertigo. Occasional hematological changes including eosinophilia, leukopenia, thrombopenia and hemolytic anemia, and transient elevation of serum transaminase, elevation of alkaline phosphatase, bilirubin, blood urea nitrogen and creatinine may occur. In most cases these reactions will reverse spontaneously or disappear after drug discontinuation. Long-term use of the product will lead to overgrowth of insensitive bacteria and cause super-infection such as candidiasis and vaginitis. Pseudocolenteric enteritis and coagulopathy can rarely occur.

Local side effect: Local administration may lead to injection site pain and induration. In rare cases, phlebitis occurs after intravenous administration, which can be reduced by slowing down the speed of intravenous injection (2 - 4 min). The intramuscular injection may cause pain in the absence of lidocaine.

4.9. Overdose

In case of overdose, hemodialysis or peritoneal dialysis will not reduce plasma concentration. There is no specific antidote. Symptomatic treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological action Cefatriaxone is a long-acting and broad spectrum cephalosporin, which exerts antibacterial activity by inhibiting synthesis of cell wall. It has potent bactericidal effect on both Gram-positive and Gram-negative bacteria. Cefatriaxone has high stability against β-lactamase (including panicillinase and cephalosporinase). In vitro and clinical trials manifested that ceftriaxone sodium exhibited high antibacterial activity against the following Gram-negative bacilli: enterobacteria including Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, indole-positive Proteus, Salmonella, Shigella and Haemophilus influenzae; good antibacterial effect against Gram-negative cocci including meningococcus and gonococcus; sensitive to Gram-positive cocci including pneumococcus, Streptococcus

pyogenes, Streptococcus viridans and Streptococcus bovis; certain antibacterial effect against Staphylococcus aureus. However the antibacterial effect was inferior to that against foregoing Gram-positive cocci. The sensitivity to Pseudomonas aeruginosa and Acinetobacter is poor. Ceftriaxone sodium also has antibacterial activity against some anaerobe including bacteroides fragilis, clostridium and peptococcus.

Toxicological study Carcinogenicity study of ceftriaxone has not been carried out. Genetic toxicity tests including Ames test and in vitro chromosomal aberration test in human lymphocytes indicated that the product had no mutagenicity. Intravenous injection of ceftriaxone 586 mg/kg/d, once daily in rats (approximately 20 folds of human dose) had no impact on the fertility. Grit calcium deposition of ceftriaxone was found in gallbladder of dogs (100 mg/kg/d for 4 weeks) and baboons (335 mg/kg/d for 6 months) following use of the product, which has a relative lower incidence in human.

5.2. Pharmacokinetic properties

Distribution After intravenous injection, ceftriaxone can quickly permeates in tissues and body fluids with apparent volume of distribution of 7 - 12 L. Single-dose administration of 1 - 2g of cefatriaxone can reach effective concentration in more than 60 tissues and body fluids including lung, heart, liver, tonsil, middle ear and nasal mucosa, skeleton, cerebrospinal fluid, prostatic fluid and synovial fluid, and maintains the bactericidal effect against sensitive bacteria for 24 hours. Cefatriaxone penetrates the infected meninges of neonatus, infants and children. Neonatus and infants receiving 50 - 100 ml per kilogram of cefatriaxone by body weight by intravenous injection, cefatriaxone concentration reaches peak in cerebrospinal fluid after 4 h with an average of 18 mg/L and is more than 1.4 mg/L after 24 h. The average dispersion in cerebrospinal fluid accounted for 17% of plasma concentration in the case of bacterial meningitis while only 4% in the case of aseptic meningitis. Adult patients with meningitis should be given 50 mg per kilogram of cefatriaxone by body weight and the concentration in cerebrospinal fluid within 2 - 24 h was several times higher than that of minimum inhibitory concentration in the most common meningitis. Cefatriaxone can pass through placental barrier and there is also small portion secreted in the milk. *Protein binding* Cefatriaxone can reversibly bind to albumin and its binding rate decreases with the increase of drug concentration. For instance, the protein binding rate is 95% when plasma concentration < 25 mg/L while it decreases to 85% when the plasma concentration is 300 mg/L. There are fewer albumins in interstitial fluid, therefore the content of free cefatriaxone in interstitial fluid is higher than that in plasma. Eliminated cefatriaxone is not decomposed and metabolized in the body and only intestinal strains turn to inactive metabolites. The total plasma clearance is 10 - 22 ml/min and renal clearance is 5 - 12 mL/min. 50 - 60% of cefatriaxone was excreted in unchanged form in urine, 40 - 50% is excreted in unchanged form in bile and finally excreted in feces as inactive metabolites. The elimination half-life in adults was approximately 8 hours.

Pharmacokinetics in special clinical setting In neonatus, 70% of dose was eliminated in urine. The average elimination half-life in infants within 8 days and elderly people aged over 75 years is normally 2 - 3 times of that of young people. For patients with hepatic or renal insufficiency, the pharmacokinetics of cefatriaxone altered a little and only the half-life extended slightly. In case of renal insufficiency, the bile duct clearance increases; in case of hepatic insufficiency, the renal clearances increases. Hemodialysis cannot increase the clearance of cefatriaxone significantly.

5.3. Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Not applicable.

6.2. Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned in section 6.6. In particular diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole andaminoglycosides. The product has many incompatibilities and therefore should be given separately.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C. Keep the vials in the original packaging in order to protect from light.

6.5. Nature and contents of container

Ceftriaxone Sodium powders for solution for injection or infusion is packaged in a 10 mL vial made of molded soda-lime glass, coated with a halogenated butyl rubber stopper and an aluminum-plastic cap.

6.6. Instructions for use and handling

Intramuscular injection: 1.0 g of the product is dissolved in 3.5 ml of 1% Lidocaine hydrochloride for intramuscular injection. It is preferred to inject at relatively larger muscle site and it is not recommended to inject more than 1 g in muscle at the same site. Lidocaine solution must not be given by intravenous injection.

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Due to potential drug immiscibility, the product cannot be mixed with other drugs and it should be administrated separately in case of combined medication. Freshly prepare the solution and use immediately.

7. MARKETING AUTHORISATION HOLDER

Shandong Luoxin Pharmaceutical Group Stock Co., Ltd.

Address: Luoqi Road, Linyi High and New Technology Industries Development Zone, Shandong Province, PR China

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

07407/08049/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION

May 13, 2022

10. DATE OF REVISION OF THE TEXT