LEBACEF®

Ceftriaxone

Composition
Each vial contains:
Active ingredient: Sterile ceftriaxone sodium equivalent to 0.5 g/1 g/2 g of ceftriaxone.
Lebacef contains 3.6 mmol of sodium per gram of ceftriaxone.

Indications
Infections caused by pathogens which are susceptible to ceftriaxone, including:
- Respiratory tract infections, particularly pneumonia, and ear, nose and throat infections
- Abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts)
- Renal and urinary tract infections
- Infections of the genital organs, including gonorrhea
- Sepsis
- Infections of the bones, joints, soft tissue and skin, and wound infections
- Infections in patients with impaired immune response
- Meningitis
- Disseminated Lyme borreliosis (stages II and III)

Perioperative prophylaxis of infections in operations on the gastrointestinal tract, biliary tract and urogenital tract and in gynecological procedures, but only in cases of potential or known contamination.
Official recommendations on appropriate use of antibiotics should be observed, in particular recommendations on how to prevent increased antibiotic resistance.

Dosage and administration
Dosage
Adults and children over 12 years old:
The usual dosage is 1-2 g of **Lebacef**, administered once daily (every 24 hours).
In severe cases or in infections caused by only moderately sensitive organisms, the dosage may be raised to 4 g administered once daily.
Neonates, infants and children up to 12 years old:
The following dosage guidelines are recommended for once-daily administration:
Neonates (up to 14 days): A daily dose of 20-50 mg/kg bodyweight; 50 mg/kg should not be exceeded.
It is not necessary to differentiate between premature infants and those born at term.
Infants and children (15 days to 12 years): A daily dose of 20-80 mg/kg.
For children with a bodyweight of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of 50 mg or more per kg bodyweight should be given by slow infusion over at least 30 minutes.
Elderly patients: The dosages recommended for adults require no modification in the case of geriatric patients.
Duration of therapy
The duration of therapy varies with the indication and the course of the disease.
Combination therapy
Synergy between **Lebacef** and aminoglycosides has been demonstrated with many Gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, combination should be considered in severe, life-threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Because of physical incompatibility, the two drugs must be administered separately at the recommended dosages.
Special dosage recommendations
Meningitis: In the case of bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily.
Once the pathogen has been identified and its sensitivity determined, the dosage can be reduced accordingly. Best results have been achieved with the following durations of therapy:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days

Lyme borreliosis: The dosage in Lyme borreliosis is 50 mg/kg up to a maximum of 2 g in children and adults, administered once daily for 14 days.
Gonorrhea: For the treatment of gonorrhea (penicillinase-producing and non-penicillinase producing strains), a single I.M. dose of 0.25 g **Lebacef** is recommended.
Perioperative prophylaxis: To prevent postoperative infections in contaminated or potentially contaminated operations, a single dose of 1-2 g **Lebacef** - depending on the risk of infection - is recommended for administration 30-90 minutes prior to surgery. In colorectal surgery, simultaneous administration of **Lebacef** and a 5-nitroimidazole, e.g. ornidazole, has proven effective.
Impaired renal and hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of **Lebacef** provided hepatic function is intact. However, in cases of preterminal renal failure (creatinine clearance < 10 ml/min) the daily dose of **Lebacef** should not exceed 2 g.
In dialysis patients no additional administration is required following dialysis. Rather, plasma concentrations in these patients should be monitored, as the elimination rate may be reduced.
The daily dose should not exceed 2 g in dialysis patients.
In patients with liver damage, there is no need for the dosage of **Lebacef** to be reduced provided renal function is intact.
In concomitant severe renal and hepatic dysfunction, plasma concentrations of ceftriaxone should be determined at regular intervals. Dose adjustments may become necessary, as the elimination rate in these patients may be reduced.
Directions for use
Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (25ºC) or 24 hours at temperatures between 2-8ºC. As a general rule, however, reconstituted solutions should be used immediately after preparation.
They range in colour from pale yellow to amber, depending on the concentration. This characteristic of the active ingredient is of no significance for the efficacy or tolerability of the drug.
Intramuscular injection: For I.M. injection, **Lebacef** 0.5 g is dissolved in 2 ml, and **Lebacef** 1 g in 3.5 ml, of 1% lidocaine solution and injected well within a relatively large mass of muscle. It is recommended that not more than 1 g be injected at one site.
The lidocaine-containing solution must never be administered intravenously.
Intravenous injection: For I.V. injection, **Lebacef** 0.5 g is dissolved in 5 ml, and **Lebacef** 1 g in 10 ml, water for injection and injected intravenously over a period of 2-4 minutes.
Intravenous infusion: The infusion should last at least 30 minutes. For I.V. infusion, 2 g **Lebacef** is dissolved in 40 ml of one of the following calcium-free infusion solutions: physiological solution, glucose 5%, glucose 10 %, levulose 5%, dextran 6% in glucose.
Ceftriaxone 2 g and ornidazole 1 g are physically and chemically compatible in 250 ml physiological sodium chloride or glucose solution.

Incompatibilities
Lebacef solutions should not be mixed with or piggy-backed into solutions containing other antibiotics. Similarly, they must not be added to diluent solutions other than those listed in "Directions for use".
Lebacef should not be added to calcium-containing solutions such as Hartmann's solution or Ringer's solution.
Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Contraindications
Ceftriaxone is contraindicated for patients with known hypersensitivity to the cephalosporin class of antibiotics. It should be avoided also in patients with a history of immediate hypersensitivity reaction to penicillins.
Ceftriaxone is contraindicated in the case of:
- Hyperbilirubinemic neonates and premature infants, because ceftriaxone induced bilirubin displacement from its binding to serum albumin causes a risk of bilirubin encephalopathy.
- Parenteral calcium therapy in neonates, because precipitation of ceftriaxone calcium salts causes a risk of fatal organ damage to kidneys and lungs.

Contraindications of lidocaine hydrochloride must be excluded before intramuscular injection of ceftriaxone when lidocaine hydrochloride is used as a solvent.

Warnings and precautions
Even after thorough history-taking, the possibility of anaphylactic reactions cannot be excluded. Should allergic reactions occur, **Lebacef** must be discontinued immediately and appropriate therapy initiated.
Ceftriaxone may prolong prothrombin time. Prothrombin time should therefore be checked if vitamin K deficiency is suspected.
In severe and persistent diarrhea, the possibility of potentially life-threatening antibiotic-induced pseudomembranous colitis must be considered. Therefore, in such cases **Lebacef** must be discontinued immediately and appropriate therapy initiated.
Antiperistaltic drugs are contraindicated in this case.
During long-term use of **Lebacef**, non-susceptible microorganisms may become difficult to control. Close patient supervision is therefore essential. Appropriate measures must be taken if superinfection occurs during treatment.
False-positive Coombs' tests have been reported during treatment with cephalosporins, as well as false-positive reaction for glucose in the urine may occur as a result of administration of ceftriaxone.
Shadows that may be mistaken for gallstones have been detected in ultrasound scans of the gallbladder. Such shadows generally consist of precipitates of the calcium salt of ceftriaxone. These precipitates usually occur following doses higher than the recommended dose. The shadows disappear on completion or discontinuation of **Lebacef** therapy.
Rarely, these findings have been associated with symptoms. In symptomatic cases conservative, nonsurgical management is recommended. Discontinuation of **Lebacef** in symptomatic cases should be at the discretion of the doctor.
Rare cases of pancreatitis possibly due to cholestasis have been reported in patients treated with ceftriaxone. At interview most of the patients concerned were found to have risk factors for cholestasis and biliary sludge, e.g. extensive previous treatment, serious disease or total parenteral nutrition. The possibility that gallbladder precipitates due to **Lebacef** may act as triggers or cofactors cannot be ruled out.
Ceftriaxone can displace bilirubin from its binding to serum albumin. Treatment of hyperbilirubinemic neonates is therefore contraindicated (see Contraindications).
Blood counts should be performed at regular intervals during prolonged treatment.
Caution is advised in patients with impaired renal function receiving concomitant treatment with aminoglycosides and diuretics.
Ceftriaxone must not be mixed or administered concurrently with calcium-containing solutions, even if the solutions are given via different infusion lines. Cases of fatal reactions due to calcium ceftriaxone precipitates in lungs and kidneys have been described in neonates, even when different infusion lines and times of administration were used for ceftriaxone and the calcium-containing solutions. For this reason intravenous calcium-containing solutions must not be administered to neonates for at least 48 hours after the last dose of **Lebacef** (see Contraindications).
Cases of intravascular ceftriaxone calcium precipitation after concomitant use of ceftriaxone with intravenous calcium-containing solutions have not been reported in other age groups.
Nevertheless, coadministration should be avoided in all patients.
In case a lidocaine solution is used as solvent, ceftriaxone solutions should only be used for intramuscular injection.
Each gram of **Lebacef** contains approximately 3.6 mmol sodium. To be taken into consideration by patients on a controlled sodium diet.

Pregnancy and lactation
Pregnancy: Ceftriaxone crosses the placental barrier. No controlled clinical studies are available.
Although no evidence of teratogenicity was detected in the relevant preclinical studies, **Lebacef** should only be used in pregnancy, particularly in the first three months, if there is a compelling indication for its use.
Lactation: As ceftriaxone is excreted - albeit in low concentrations - in breast milk, **Lebacef** should not be used by nursing mothers. Where treatment is absolutely essential, breastfeeding should be stopped.

Driving and using machines
Since **Lebacef** may induce dizziness, the ability to drive and operate machines may be impaired.

Undesirable effects
The following undesirable effects, which subsided either spontaneously or after withdrawal of the drug, have been observed during the use of ceftriaxone:
Infections: Rare: mycosis of the genital tract, superinfection with non-susceptible organisms.
Blood and lymphatic system: Common: eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, prolongation of prothrombin time. Rare: elevation of serum creatinine. Very rare: coagulation disorders. Very rarely, cases of agranulocytosis (< 500/mm³) have been observed, mostly following a total dose of 20 g or more.
Blood counts should be performed at regular intervals during prolonged treatment. Slight prolongation of prothrombin time has been reported.
Gastrointestinal disturbances: Common: loose stools/diarrhea, nausea, vomiting, stomatitis, glossitis. Rare: pancreatitis, possibly due to bile duct obstruction. Most of the patients concerned had risk factors for cholestasis and biliary sludge, e.g. preceding major surgery, serious disease or total parenteral nutrition. The possibility that **Lebacef** may act as a trigger or cofactor in the formation of gallbladder precipitates cannot be ruled out. Very rare: Pseudomembranous enterocolitis.
Liver and gallbladder: Very common: symptomless precipitation of ceftriaxone calcium salt in the gallbladder of children, reversible cholelithiasis in children. This disorder occurs rarely in adults (see Warnings and precautions). Common: increase in serum liver enzymes (AST [SGOT], ALT [SGPT], alkaline phosphatase).
Skin: Common: rash, allergic dermatitis, pruritus, urticaria, edema. Very rare: severe skin reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis).
Kidneys and urinary tract: Rare: oliguria. Very rare: renal precipitates have been reported, mostly in children aged over 3 years who were treated with either high daily doses (e.g.≥80 mg/kg/day) or total doses in excess of 10 g and who had additional risk factors (e.g. reduced fluid intake, confinement to bed, etc.). This side effect may or may not give rise to clinical manifestations, can lead to renal failure, and is reversible after discontinuation of **Lebacef** therapy.
General disturbances and administration site reactions: Rare: headache, dizziness, fever, chills. Anaphylactic or anaphylactoid reactions. Vein wall inflammatory reactions after I.V. administration. These may be minimized by slow (2-4 minutes) injection of the substance.
Intramuscular injection without lidocaine solution is painful.

Overdosage
Excessive plasma concentrations of ceftriaxone cannot be reduced by hemodialysis or peritoneal dialysis. Symptomatic measures are recommended for the treatment of patients following overdosage.

Interactions
No impairment of renal function has been observed after simultaneous administration of large doses of ceftriaxone and potent diuretics such as furosemide. No disulfiram-like effect has been demonstrated following administration of ceftriaxone and ingestion of alcohol. Ceftriaxone does not contain the N-methylthiotetrazole moiety that has been associated with ethanol intolerance and bleeding problems with use of certain other cephalosporins.
Probenecid does not influence the elimination of ceftriaxone.
There is no evidence that ceftriaxone increases the renal toxicity of aminoglycosides. Nevertheless, the two products must be administered separately (see Incompatibilities).
Bacteriostatic drugs can interfere with the bactericidal action of cephalosporins.
Antagonistic effects were observed in an *in vitro* study of ceftriaxone in combination with chloramphenicol.

Pharmacodynamics
The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms. Ceftriaxone has a long serum half-life and it is highly stable to most β-lactamases and both penicillinases and cephalosporinases of Gram-positive and Gram-negative bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications):
Gram-positive aerobes: *Staphylococcus aureus* (including penicillinases-producing strains), *Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* group A *(Str. pyogenes), Streptococcus* group B *(Str. agalactiae), Streptococcus viridans, Streptococcus bovis.*
Note: Methicillin-resistant *Staphylococcus* spp. are resistant to cephalosporins, including ceftriaxone. Most strains of Enterococci (e.g. *Entrtococcus faecalis*) are resistant.
Gram-negative aerobes: *Aeromonas* spp., *Alcaligenes* spp., *Branhamella catarrhalis* (β-lactamase negative and positive), *Citrobacter* spp., *Enterobacter* spp. (some strains are resistant), *Escherichia coli, Haemophilus ducreyi, Haemophilus influenzae* (including penicillinase-producing strains), *Haemophilus parainfluenzae, Klebsiella* spp. (including *Kl. pneumoniae*), *Moraxella* spp., *Morganella morganii, Neisseria gonorrheae* (including penicillinase-producing strains), *Neisseria meningitidis, Plesiomonas shigelloides, Proteus mirabilis, Proteus vulgaris, Providencia* spp., *Pseudomonas aeruginosa* (some strains are resistant), *Salmonella* spp. (including S. typhi), *Serratia* spp. (including *S. marcescii* spp.), *Shigella* spp., *Vibrio* spp. (including *V. cholerae*), *Yersinia* spp. (including *Y. enterocolitica*).
Note: Many strains of the above microorganisms that are multiply resistant to other antibiotics, e.g. penicillins, older cephalosporins and aminoglycosides are susceptible to ceftriaxone. *Treponema pallidum* is sensitive *in vitro* and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy.
Anaerobic organisms: *Bacteroides* spp. (including some strains of *B. fragilis*), *Clostridium* spp. (except *Cl. difficile*), *Fusobacterium* spp. (except *F. mortiferum* and *F. varium*), *Peptococcus* spp., *Peptostreptococcus* spp.
Note: Many strains of β-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant.

Pharmacokinetics
The pharmacokinetics of ceftriaxone are nonlinear.
Absorption: After a single I.M. injection of 1 g ceftriaxone, a peak plasma concentration of 81 mg/l was reached after 2-3 h. After a single I.V. infusion of 1 g, a concentration of 168.1 ± 28.2 mg/l was reached after 30 min. After a single I.V. infusion of 2 g, a concentration of 256.9 ± 16.8 mg/l was reached after 30 min.
The areas under the plasma-concentration-time curves after I.V. and I.M. administration are identical. This means that the bioavailability of intramuscularly administered ceftriaxone is 100%.
Distribution: The distribution volume is between 7 and 12 liters.
On intravenous administration ceftriaxone diffuses rapidly into interstitial body fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.
Ceftriaxone is reversibly bound to albumin, the degree of binding decreases with increasing concentration. Thus, binding decreases from 95% at a plasma concentration of < 100 mg/l to 85% at 300 mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children.
The average concentration in CSF during bacterial meningitis is 17% of the plasma concentration; in aseptic meningitis it is 4%. 24 hours after I.V. injection of **Lebacef** in doses of 50-100 mg/kg bodyweight, ceftriaxone concentrations > 1.4 mg/l were measured in CSF.
In adult patients with meningitis, administration of 50 mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common causative organisms of meningitis.
Metabolism: Ceftriaxone is not metabolized in the organism itself. Only following biliary excretion into the intestinal lumen does the intestinal flora transform the active ingredient into inactive metabolites.
Elimination: Plasma clearance is 10-22 ml/min. Renal clearance is 5-12 ml/min. 50-60% of ceftriaxone is excreted unchanged via the kidneys, while 40-50% is excreted unchanged in the bile. The plasma half-life in adults is about 8 hours.
Pharmacokinetics in special patient groups: In neonates, renal elimination accounts for about 70% of the dose.
In infants aged less than 8 days and in persons aged over 75 years, the average plasma half-life is approximately 2-3 times that in healthy young adults.
In patients with mild to moderate renal failure or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only slightly altered. The plasma half-life is minimally increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased, whereas if liver function alone is impaired, renal elimination is increased.

Presentation

Lebacef 0.5 g for I.M. injection:
OPAT Kit: 1 vial containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone, 1 solvent ampoule containing 2 ml lidocaine solution (lidocaine hydrochloride 1%), sterile syringe, 2 needles, sterile alcohol swab, adhesive bandage.
Lebacef 0.5 g for I.V. injection:
OPAT Kit: 1 vial containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone, 1 solvent ampoule containing 5 ml water for injection, sterile syringe, 2 needles, sterile alcohol swab, adhesive bandage.
Lebacef 0.5 g for I.M./I.V. injection:
Pack of 10 vials each containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone.
Lebacef 1 g for I.M. injection:
OPAT Kit: 1 vial containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone, 1 solvent ampoule containing 3.5 ml lidocaine solution (lidocaine hydrochloride 1%), sterile syringe, 2 needles, sterile alcohol swab, adhesive bandage.
Lebacef 1 g for I.V. injection:
OPAT Kit: 1 vial containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone, 1 solvent ampoule containing 10 ml water for injection, sterile syringe, 2 needles, sterile alcohol swab, adhesive bandage.
Lebacef 1 g for I.M./I.V. injection:
Pack of 10 vials each containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone.
Lebacef 2 g for I.V. infusion:
Pack of 1 or 10 vials each containing sterile powder of ceftriaxone sodium equivalent to 2 g of ceftriaxone.

Expiry date and storage conditions

See the expiry date printed on the outer carton.
This date refers to the product correctly stored in unopened package.
Beware not to use **Lebacef** after this date.
Store below 30°C. Protect from light and heat.
Keep all medicines out of reach of children.

Manufactured by: **Mitim S.R.L.**
Brescia, Italy
For: **ARWAN Pharmaceutical Industries Lebanon s.a.l.**
Jadra, Lebanon

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists