

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Lebacef 0.5 g Sterile powder for solution for injection

Lebacef 1 g Sterile powder for solution for injection

Lebacef 2g Sterile powder for solution for infusion

2. Qualitative and quantitative composition

Each 0.5 g vial contains 0.596 g ceftriaxone sodium equivalent to 0.5 g of ceftriaxone.

Each 1 g vial contains 1.193 g ceftriaxone sodium equivalent to 1 g of ceftriaxone.

Each 2 g vial contains 2.386 g ceftriaxone sodium equivalent to 2 g of ceftriaxone.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile powder for solution for injection Sterile powder for solution for injection Sterile powder for solution for infusion

4. Clinical particulars

4.1 Therapeutic indications

Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active in vitro against a wide range of Gram-positive and Gram-negative organisms, which include β -lactamase producing strains. Ceftriaxone is indicated in the treatment of the following 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, recommendations on how to prevent increased antibiotic resistance.

4.2 Posology and method of administration

A solvent containing lidocaine is used for intramuscular (i.m.) administration. Therefore, any contraindications to lidocaine must first be excluded before i.m. injection of ceftriaxone. Lebacef may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose - or, in the specified indications, a single dose - will give satisfactory therapeutic results. 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. Lebacef is contraindicated in premature neonates up to postmenstrual age of 41 weeks (gestational age + postnatal age). Lebacef is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as in parenteral nutrition, because of the risk of calcium ceftriaxone precipitation. 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 in infants and children up to 12 years of age should be given by slow infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. Elderly patients: The dosages recommended for adults require no modification in the case of geriatric patients, provided there is no severe renal and hepatic impairment. 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 chemical incompatibility between Lebacef and aminoglycosides, the two drugs must be administered separately at the recommended dosages. Chemical incompatibility with Lebacef has also been observed with intravenous administration of amsacrine, vancomycin and fluconazole. 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. Ceftriaxone is not eliminated by peritoneal or hemodialysis. Dialysis patients therefore require no supplementary dosing following dialysis. 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. Patients with severe renal and hepatic impairment in concomitant severe renal and hepatic dysfunction, clinical monitoring of safety and efficacy is advised.

Method of administration

Intramuscular administration

Lebacef can be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site.

As the solvent used is lidocaine, the resulting solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.

Intravenous administration

Lebacef can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section 4.3 and 4.4). Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium (see section 4.3).

Diluents containing calcium, (e.g. Ringer's solution or 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. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30- 90 minutes prior to surgery.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

Ceftriaxone is contraindicated in:

Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) *

Full-term neonates (up to 28 days of age):

- with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are

conditions in which bilirubin binding is likely to be impaired*

- if they require (or are expected to require) intravenous calcium treatment, or calcium-

containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.8 and 6.2).

- In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin

binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (see section 4.4).

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported; however, the frequency of these events is not known (see section 4.8).

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may

be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2).

Paediatric population

Safety and effectiveness of Lebacef in neonates, infants and children have been established for the dosages described under Posology and Method of Administration (see section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Lebacef is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section 4.3).

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Lebacef (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during Lebacef treatment in both adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Long term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftriaxone (see section 4.8).

Discontinuation of therapy with ceftriaxone and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Severe renal and hepatic insufficiency

In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised (see section 4.2).

Interference with serological testing

Interference with Coombs tests may occur, as Lebacef may lead to false-positive test results. Lebacef can also lead to false-positive test results for galactosaemia (see section 4.8).

Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with Lebacef should be done enzymatically (see section 4.8).

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

Sodium

Each gram of Lebacef contains 3.6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section 4.2). In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine

In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use (see section 4.3). The lidocaine solution should never be administered intravenously.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with Lebacef (see section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of Lebacef-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Lebacef vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone (see section 4.8).

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

In patients treated with ceftriaxone, the Coombs' test may lead to false-positive test results.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with ceftriaxone should be carried out enzymatically.

No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).

Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

4.6 Pregnancy and lactation

Pregnancy: Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development (see section 5.3). Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Lactation: Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility: Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100 - < 1/10$)

Uncommon ($\geq 1/1000 - < 1/100$)

Rare ($\geq 1/10000 - < 1/1000$)

Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known a
Infections and infestation s		Genital fungal infection	Pseudomembranous colitisb	Superinfectionb
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemiab Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity b
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory , thoracic and mediastinal disorders			Bronchospasm	

Gastrointestinal disorders	Diarrhoeab Loose stools	Nausea Vomiting		Pancreatitisb Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitationb Kernicterus
Skin and subcutaneous	Rash	Pruritus	Urticaria	Stevens Johnson Syndromeb

tissue disorders				Toxic epidermal necrolysis ^b Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive ^b Galactosaemia test false positive ^b Non enzymatic methods for glucose determination false positive ^b

a Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

b See section 4.4

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via the pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS): <https://pv.pharmacyboardkenya.org>

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins, ATC code: J01DD04.

Mode of action

Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Resistance

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs),

carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.

- reduced affinity of penicillin-binding proteins for ceftriaxone.
- outer membrane impermeability in Gram-negative organisms.
- bacterial efflux pumps.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	Dilution Test (MIC, mg/L)	
	Susceptible	Resistant
Enterobacteriaceae	≤ 1	> 2
Staphylococcus spp.	a.	a.
Streptococcus spp.	b.	b.

- Susceptibility inferred from cefoxitin susceptibility.
- Susceptibility inferred from penicillin susceptibility.
- Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.
- Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species Gram-positive aerobes

Staphylococcus aureus (methicillin-susceptible) £

Staphylococci coagulase-negative (methicillin-susceptible) £

Streptococcus pyogenes (Group A)

Streptococcus agalactiae (Group B)

Streptococcus pneumoniae

Viridans Group *Streptococci*

Gram-negative aerobes

Borrelia burgdorferi

Haemophilus influenzae

Haemophilus parainfluenzae

Moraxella catarrhalis

Neisseria gonorrhoea

Neisseria meningitidis

Proteus mirabilis

Providencia spp

Treponema pallidum

Species for which acquired resistance may be a problem Gram-positive aerobes

Staphylococcus epidermidis+

Staphylococcus haemolyticus+

Staphylococcus hominis+

Gram-negative aerobes

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli%

Klebsiella pneumoniae%

Klebsiella oxytoca%

Morganella morganii

Proteus vulgaris

Serratia marcescens

Anaerobes

Bacteroides spp.

Fusobacterium spp.

Peptostreptococcus spp.

Clostridium perfringens

Inherently resistant organisms' Gram-positive aerobes

Enterococcus spp.

Listeria monocytogenes

Gram-negative aerobes

Acinetobacter baumannii

Pseudomonas aeruginosa

Stenotrophomonas maltophilia

Anaerobes

Clostridium difficile

Others:

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Legionella spp.

Ureaplasma urealyticum

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

+ Resistance rates >50% in at least one region

% ESBL producing strains are always resistant

5. 2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural,

prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (C_{max}) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in

patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two-fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

In older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Paediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with in vivo efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

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

None.

6.2 Incompatibilities

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides and labetalol.

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).

6.3 Shelf life

36 months. For shelf life of diluted product see section 6.6.

6.4 Special precautions for storage

See the expiry date printed on the outer carton. This date refers to the product stored correctly in unopened package. Beware not to use Lebacef after this date. Store below 30°C. Protect from light and heat. For shelf life of diluted product see section 6.6.

6.5 Nature and contents of container

Lebacef 0.5 g and 1 g: neutral type III Ph. Eur 15 ml glass vial with bromobutylic rubber stopper and aluminium seal, containing a sterile almost white or yellowish crystalline powder. 2 ml solvent is marketed in a 3 ml glass ampoule; 3.5 ml solvent is marketed in a 4 ml glass ampoule; 5 ml solvent is marketed in a 5 ml glass ampoule; 10 ml solvent is marketed in a 10 ml glass vial. All the solvent ampoules are made off neutral type I Ph. Eur glass with high hydrolytic resistance. Lebacef 2 g: neutral type II Ph. Eur 50 ml glass vial with bromobutylic rubber stopper and aluminium seal, containing a sterile almost white or yellowish crystalline powder.

Packs 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, two 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, needle, cannula butterfly, sterile alcohol swab, adhesive bandage. Lebacef 0.5 g for I.M. injection: Pack of 10 vials each containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone. Lebacef 0.5 g for 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, two 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, needle, cannula butterfly, sterile alcohol swab, adhesive bandage. Lebacef 1 g for I.M. injection: Pack of 10 vials each containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone. Lebacef 1 g for 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.

6.6 Special precautions for disposal and other handling

Directions for use Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (25°C) or 24 hours at temperatures between 2-8°C. 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.

7. Marketing authorisation holder

Arwan Pharmaceutical Industries Lebanon s.a.l
Jadra Alchouf, Mount Lebanon, P.O. Box: 613 – Saida

8. Marketing authorisation number

H2021/CTD8142/16156

9. Date of first authorisation/renewal of the authorisation

2021 September 01

10. Date of revision of the text

2021 September 01