Summary of Product Characteristics

1. Name of the medicinal product

Lebacef 0.5g Sterile powder for solution for injection
Lebacef 1 g Sterile powder for solution for injection

Lebacef 2 g 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.

3. Pharmaceutical form

Sterile almost white or yellowish crystalline powder for solution for injection
Sterile almost white or yellowish crystalline powder for solution for injection
Sterile almost white or yellowish crystalline powder for solution for infusion
The reconstituted solutions range in color from pale yellow to amber, depending on the concentration.

4. Clinical particulars

4.1 Therapeutic indications

Lebacef is indicated for the treatment of the following infections in adults and children including term neonates (from birth):

- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Lebacef may be used:

- For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults
- For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age
- For Pre-operative prophylaxis of surgical site infections
- In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
- In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Lebacef should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).
Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.
The doses recommended in the tables below are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

Adults and children over 12 years of age (≥ 50 kg)

Ceftriaxone dosage*	**Treatment frequency****	**Indications**
1-2 g	Once daily	Community acquired pneumonia
		Acute exacerbations of chronic obstructive pulmonary disease
		Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Hospital acquired pneumonia
		Complicated skin and soft tissue infections
		Infections of bones and joints
2-4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial endocarditis

		Bacterial meningitis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.
** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for adults and children over 12 years of age (≥ 50 kg) that require specific dosage schedules:

Acute otitis media

A single intramuscular dose of Lebacef 1-2 g can be given.

Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Lebacef may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

Pre-operative prophylaxis of surgical site infections 2 g as a single pre-operative dose.

Gonorrhoea

500 mg as a single intramuscular dose.

Syphilis

The generally recommended doses are 500 mg-1 g once daily increased to 2 g once daily for neurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

2 g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Paediatric population

Neonates, infants and children 15 days to 12 years of age (< 50 kg)

For children with bodyweight of 50 kg or more, the usual adult dosage should be given.

Ceftriaxone dosage*	**Treatment frequency****	**Indications**
50-80 mg/kg	Once daily	Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
50-100 mg/kg (Max 4 g)	Once daily	Complicated skin and soft tissue infections
		Infections of bones and joints

		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)	Once daily	Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for infants and children 15 days to 12 years (< 50 kg) that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Lebacef 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, Lebacef may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

Pre-operative prophylaxis of surgical site infections 50-80 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Neonates 0-14 days

Lebacef is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Ceftriaxone dosage*	**Treatment frequency**	**Indications**
20-50 mg/kg	Once daily	Intra-abdominal infections
		Complicated skin and soft tissue infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
		Infections of bones and joints

		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
50 mg/kg	Once daily	Bacterial meningitis
		Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered. A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days that require specific dosage schedules:

Acute otitis media
For initial treatment of acute otitis media, a single intramuscular dose of Lebacef 50 mg/kg can be given.

Pre-operative prophylaxis of surgical site infections 20-50 mg/kg as a single pre-operative dose.

Syphilis
The generally recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Duration of therapy
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.

Older people
The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.

Patients with hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.
There are no study data in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone, provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min), should the ceftriaxone dosage not exceed 2 g daily.
In patients undergoing dialysis no additional supplementary dosing is required

following the dialysis.
Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

Patients with severe renal and hepatic impairment
In patients with both severe renal and hepatic dysfunction, close 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). Accidental intravenous injection should be checked for by aspiration of the syringe before injection. 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.
- 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). See information in the Summary of Product Characteristics of lidocaine, especially contraindications.

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 and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal have been reported in association of ceftriaxone treatment; 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 ceftriaxone 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 ceftriaxone (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during ceftriaxone 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 83 mg (3.6 mmol) of sodium per gram of ceftriaxone, corresponding to 4.2% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

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 ceftriaxone (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 ceftriaxone-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.

Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self – limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

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 Fertility, 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.

Breastfeeding:
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 breastfeeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breastfeeding 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 (≥1/10)
- Common (≥ 1/100 - < 1/10)
- Uncommon (≥ 1/1000 - < 1/100)
- Rare (≥ 1/10000 - < 1/1000)
- Not known (cannot be estimated from the available data)

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known[a]**
Infections and infestations		Genital fungal Infection	Pseudomembranous colitis[b]	Superinfection[b]
Blood and lymphatic syste	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis

m				
disorders				
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b] Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache Dizziness	Encephalopathy	Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus Hepatitis[c] Hepatitis cholestatic[b,c]
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS)[b]
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)

General disorders and administration site conditions		Phlebitis Injection site reactions 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

[c] Usually reversible upon discontinuation of ceftriaxone

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the hard copies of TMDA's yellow forms accessible at healthcare facility or directly to TMDA by phone call through Toll Free number 080011 0084 or send a simple short text message by just dialling *152*00# and follow the instructions.

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. (Groups A, B, C and	b.	b.

G)		
Streptococcus pneumoniae	≤ 0.5[c.]	> 2
Viridans group *Streptococci*	≤0.5	>0.5
Haemophilus influenzae	≤ 0.12[c.]	> 0.12
Moraxella catarrhalis	≤ 1	> 2
Neisseria gonorrhoeae	≤ 0.12	> 0.12
Neisseria meningitidis	≤ 0.12 [c.]	> 0.12
Non-species related	≤ 1[d.]	> 2

a. Susceptibility inferred from cefoxitin susceptibility.

b. Susceptibility inferred from penicillin susceptibility.

c. 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.

d. 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 influenza Haemophilus parainfluenzae Moraxella catarrhalis Neisseria gonorrhoea Neisseria meningitides 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.
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).
If treatment with a combination of another antibiotic with Lebacef is intended, administration should not occur in the same syringe or in the same infusion solution.

6.3 Shelf life

Unopened vials: 36 months.
Chemical and physical in-use stability of the reconstituted product has been demonstrated for 6 hours at 25°C or 24 hours at 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than the times sated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

Keep this medicine out of reach of children.
Store below 30°C. Protect from light and heat. For shelf life of reconstituted product see section 6.6.
For storage conditions of the reconstituted medicinal product, see
section 6.3. 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.
Do not use this medicine after the expiry date which is stated on the carton after "EXP. Date". The expiry date refers to the last day of that month.

6.5 Nature and contents of container Lebacef 0.5 g and 1 g:

Colourless 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.M. injection:
Pack of 1 vial containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone and 1 solvent ampoule containing 2 ml lidocaine solution (lidocaine hydrochloride 1%).

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.V. injection:
Pack of 1 vial containing sterile powder of ceftriaxone sodium equivalent to 0.5 g of ceftriaxone and 1 solvent ampoule containing 5 ml water for injection.

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, 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.V. injection:
Pack of 1 vial containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone and 1 solvent ampoule containing 10 ml water for injection.

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 1 g for I.M. injection:
Pack of 1 vial containing sterile powder of ceftriaxone sodium equivalent to 1 g of ceftriaxone and 1 solvent ampoule containing 3.5 ml lidocaine solution (lidocaine hydrochloride 1%).

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.

Not all presentations might be marketed.

The powder is almost white to yellowish crystalline powder.

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 5 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%, levulose 5%, dextran 6% in glucose 5%. 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., No.3 Jadra real zone,
Province of El- Chouf,
Governorate of Mount Lebanon
Lebanon

8. Marketing authorisation number

H2021/CTD8126/15239

9. Date of first Authorisation/renewal of the authorization

Renewal of the authorization August 2026

10. Date of revision of the text

January, 2025