SUMMARY OF PRODUCT CHARACTERISTICS

1-NAME OF THE MEDICINAL PRODUCT (FPP)

Cetafor

Ceftriaxone

1.1 Strength

1000 mg IV, 500 mg IV, 1000 mg IM

1.2 Pharmaceutical form

Powder and solvent for solution for injection

2- QUALITATIVE AND QUANTITATIVE COMPOSITION

- Cetafor® 1000 mg IV: the vial contains 1193 mg sodium ceftriaxone equivalent to 1000 mg ceftriaxone. Solvent: 10 ml water for injection.
- Cetafor® 500 mg IV: the vial contains 596 mg sodium ceftriaxone equivalent to à 500 mg ceftriaxone. Solvent: 5 ml water for injection.
- Cetafor® 1000 mg IM: the vial contains 1193 mg sodium ceftriaxone equivalent to 1000 mg ceftriaxone. Solvent: 4 ml of Lidocaine hydrochloride 10 mg/ml (1%).

Excipients with known effect

Cetafor contains approximately 83 mg (3.6 mmol) of sodium per 1000 mg ceftriaxone.
For the full list of excipients, see section 6.1

3- PHARMACEUTICAL FORM

Powder and solvent for solution for injection

*Powde*r: Sterile white to yellowish crystalline powder

Solvents: Clear, colourless sterile solution

Solution of powder reconstituted with the solvent: Clear solution

4- CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetafor 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

Cetafor 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

Cetafor should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum.

4.2 Posology and mode of administration

4.2.1 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 **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.

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

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

(1) In documented bacteraemia, the higher end of the recommended dose range should be considered.

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

Specific dosage schedules for adults and children over 12 years of age (≥ 50 kg)

- Acute otitis media. A single intramuscular dose of Cetafor 1-2 g can be given. Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Cetafor 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 shouldbe 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.

4.2.2 Special populations

Older patients

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.

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 hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

4.2.3 Pediatric population

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

Indications	Dose of ceftriaxone (1)	Frequency (2)
Community acquired pneumonia Hospital acquired pneumonia Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis)	50-80 mg/kg	Once daily
Complicated skin and soft tissue infections of bones and joints Management of neutropenic patients with fever that is suspected to be due to a bacterial infection	50-100 mg/kg (max 4 g)	Once daily
Management of neutropenic patients with fever that is suspected to be due to a bacterial infection Bacterial endocarditis Bacterial meningitis	80-100 mg/kg (max 4 g)	Once daily

(1) In documented bacteraemia, the higher end of the recommended dose range should be considered.

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

Specific dosage schedules for neonates, infants and children 15 days to 12 years (< 50 kg)

- Acute otitis media. For initial treatment of acute otitis media, a single intramuscular dose of Cetafor 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, Cetafor may be effective when given as anintramuscular 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 onvery 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 to 14 days of age

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

Indications	Dose of ceftriaxone (1)	Frequency (2)
Intra-abdominal infections Complicated skin and soft tissue infections Complicated urinary tract infections (includingpyelonephritis) 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	20-50 mg/kg	Once daily
Bacterial endocarditis Bacterial meningitis	50 mg/kg	Once daily

(1) In documented bacteraemia, the higher end of the recommended dose range should be considered.

Specific dosage schedules for neonates 0-14 days

- Acute otitis media. For initial treatment of acute otitis media, a single intramuscular dose of Cetafor 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.

4.2.4 Method of administration

Cetafor 1000 mg IV et Cetafor 500 mg IV

- Intravenous injection
  - Cetafor 1000 mg IV should be dissolved in 10 ml of water for injection, by using the solvent ampoule included in the same box. The injection should be administered over 2-4 minutes.
  - Cetafor 500 mg IV should be dissolved in 5 ml of water for injection, by usingthe solvent ampoule included in the same box. The injection should be administered over 2-4 minutes.

- Intravenous perfusion

  Concentrations between 10mg/ml and 40 mg/ml are recommended. Cetafor 1000 IV and 500mg IV should be dissolved in one of the following solutions:

  - 0.9 % sodium chloride;
  - 5 % dextrose;
  - 10 % dextrose;
  - 5 % dextrose + 0.9 % sodium chloride;
  - 5 % dextrose + 0.45 % sodium chloride.

  All these solutions should be administered immediately after reconstitution.

Solutions containing ceftriaxone should not be mixed or added to other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution. Ceftriaxone should not be mixed or administered simultaneously with solutions containing calcium.

Cetafor 1000 mg IM

- Intramuscular injection
    - Cetafor 1000 mg IM should be dissolved in 4 ml of sterile 1% Lidocaine hydrochloride, by using the solvent ampoule included in the same box.
    - The solution should be administered by deep intragluteal injection and used immediately after reconstitution.

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).
- 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, leading to a possible risk of bilirubin encephalopathy.
- Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent in patients who have hypersensitivity to local anaesthetics and who have heart block. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warning and precautions for use

General information Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. 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.

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 andcalcium-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.

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Cetafor. Severe cases of haemolytic anaemia, including fatalities, have been reported during Cetafor 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.

Pseudo-membranous colitis

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. 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.

Overgrowth of non-susceptible microorganisms

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.

Interference with serological testing

Interference with Coombs tests may occur, as ceftriaxone may lead to false-positive test results. Ceftriaxone can also lead to false-positive test results for galactosaemia. Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with ceftriaxone should be done enzymatically. 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 Cetafor contains 3.6 mmol of sodium.

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. 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.

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ceftriaxone. 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. In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered bythe physician based on specific benefit risk assessment.

4.4.1 Pediatric population

Studies in neonates, infants and children have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Cetafor is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy.

4.5 Interactions with other medicinal products and other forms of interactions

4.5.1 General information

- Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Cetafor 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.

- 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.
- 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 closelyadhered 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-positivetest 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.

4.5.2 Additional information on special populations

No additional information

4.5.3 Pediatric population

No additional information

4.6 Pregnancy, lactation and fertility

4.6.1 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. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

4.6.2 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 sensitization should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue the treatment with ceftriaxone, taking into account the benefit of breast feeding for the child and thebenefit of therapy for the woman.

4.6.3 Fertility

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

4.7 Effects on the 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. 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.

The frequencies of adverse reactions reported with ceftriaxone are defined as:

- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to < 1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (< 1/10,000)
- not known (cannot be estimated from the available data)

Adverse events	**Frequency**
Infections and infestations	
Genital fungal infection	Uncommon
Pseudo-membranous colitis	Rare
Blood and lymphatic system disorders	
Eosinophilia - Leucopenia - Thrombocytopenia	Common

Adverse events	**Frequency**
Granulocytopenia – Anaemia - Coagulopathy	Uncommon
Haemolytic anaemia - Agranulocytosis	Not Known
Immune system disorders	
Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity	Not Known
Nervous system disorders	
Headache Dizziness	Uncommon
Convulsion	Not Known
Ear and labyrinth disorders	
Vertigo	Not Known
Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Rare
Gastrointestinal disorders	
Diarrhoea – Loose Stools	Common
Nausea - Vomiting	Uncommon
Pancreatitis – Stomatitis -Glossitis	Not Known
Hepatobiliary disorders	
Increased hepatic enzymes	Common
Gall bladder precipitation Kernicterus	Not Known
Skin and subcutaneous tissue disorders	
Rash	Common
Pruritus	Uncommon
Urticaria	Rare
Stevens Johnson Syndrome Toxic epidermal necrolysis Erythema multiforme Acute generalised exanthematous pustulosis	Not Known
Renal and urinary disorders	
Hematuria - Glycosuria	Rare
General disorders and administration site conditions	

Phlebitis Injection site pain Pyrexia	Uncommon
Oedema Chills	Rare
Investigations	
Augmentation of blood creatinine	Uncommon
Coombs test false positive	Not Known
Adverse events	**Frequency**
Galactosaemia test false positive Non enzymatic methods for glucose determination false positive	

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.

	Dilution test (MIC, mg/l)	
Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1	> 2
Staphylococcus spp.	(a)	(a)
Streptococcus spp. (Group A, B, C and G)	(b)	(b)
Streptococcus pneumoniae	≤ 0.5 (c)	> 2
Streptococci group Viridans	≤ 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) (1)
- Staphylococci coagulase-negative (methicillin-susceptible) (1)

- *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 gonorrhoeae*
- *Neisseria meningitidis*
- *Proteus mirabilis*
- *Providencia spp*
- *Treponema pallidum*

Species for which acquired resistance may be a problem

Gram positive aerobe

- *Staphylococcus epidermidis* (2)
- *Staphylococcus haemolyticus* (2)
- *Staphylococcus hominis* (2)

Gram negative aerobes

- *Citrobacter freundii*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Escherichia coli* (3)
- *Klebsiella pneumoniae* (3)
- *Klebsiella oxytoca* (3)
- *Morganella morganii*
- *Proteus vulgaris*
- *Serratia marcescens*

Anaerobes

- *Bacteroides* spp.
- *Fusobacterium* spp.
- *Peptostreptococcus* spp.
- *Clostridium perfringens*

Inherent 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*

(1) All methicillin-resistant staphylococci are resistant to ceftriaxone

(2) Resistance rates >50% in at least one region

(3) ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

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 levelsare approximately 80, 150 and 250 mg/l respectively.

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.

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 (Cmax) 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.

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 inpatients 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 proteinbinding 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
- The powder of Cetafor 1000mg IV, Cetafor 500 mg IV and Cetafor 1000 mg IM contains no excipients.
- Solvent of **Cetafor 1000 mg IV:** water for injection
- Solvent of **Cetafor 500 mg IV:** water for injection

- Solvent of **Cetafor 1000 mg IM:** lidocaine hydrochloride, sodium chloride, water for injection.

6.2 Incompatibilities

- Solutions containing Ceftriaxone should not be mixed with or added to other agents. In particular, Ceftriaxone is not compatible with calcium-containing solutions such asHartmann's solution and Ringer's solution.
- Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions.
- Based on literature reports ceftriaxone is not compatible with Amsacrine, Vancomycin, Fluconazole or Aminoglycosides and Labetalol

6.3 Shelf life

Packaged product Powder and solvent

36 months

Shelf life unopened vials: 36 months

Shelf life unopened ampoules: 60 months.

Reconstituted solutions

From a microbiological point of view, solutions should be used immediately after reconstitution.

6.4 Special precautions for storage

Cetafor 1000 mg IV, 500 mg IV and 1000 mg IM should be stored below 30°C, in original package to protect from light.
After reconstitution the solutions should be used immediately.

Nature and contents of container

- **Cetafor 1000 mg IV:** Box with one powder vial and one solvent ampoule

  Powder vial**:** colourless type III glass vial of 15 ml, closed with bromobutyl stopperand sealed with an aluminium cap.
  Solvent ampoule: colourless type I glass ampoule 10 ml (water for injection)

- **Cetafor 500 mg IV:** Box with one powder vial and one solvent ampoule.

  Powder vial: colourless type III glass vial of 10 ml, closed with bromobutyl stopperand sealed with an aluminium cap.
  Solvent ampoule: colourless type I glass ampoule 5 ml (water for injection)

- **Cetafor 1000 mg IM**: Box with one powder vial and one solvent

  Powder vial**:** colourless type III glass vial of 15 ml, closed with bromobutyl stopperand sealed with an aluminium cap.
  Solvent ampoule: colourless type I glass ampoule 4 ml (Lidocaine HCl 10 mg/ml).

6.5 Special precautions for disposal and other handlings

No special requirements for disposal.

Any unused product or waste must be disposed of in accordance with applicable regulations.

7- MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1 Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2 Manufacturers

PharmaVision Ilaç San. ve Tic. A.Ş

Davutpaşa Cad. No: 145, 34010 Topkapi-Istanbul, Turkey

Sanofi Ilaç San. ve. Tic. A.Ş (*previously Zentiva Sağlık Ürünleri San ve Tic. A.Ş*)

Küçükkarıştıran Mahalessi, 39780 Büyükkarıştıran/ Lüleburgaz/Kırklareli, Turkey

8- MARKETING AUHORISATION NUMBER

TAN 21 HM 0147

9- DATE OF FIRST REGISTRATION

29/03/2021

10- DATE OF REVISION OF TEXT

March 2021