SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CEPHTRIFECT 500 (powder for solution for injection)

CEPHTRIFECT 1 000 (powder for solution for injection)

CEPHTRIFECT 2 000 (powder for solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEPHTRIFECT 500: Each vial contains: dry, sterile ceftriaxone sodium equivalent to 0,5 g ceftriaxone.

CEPHTRIFECT 1 000: Each vial contains dry, sterile ceftriaxone sodium equivalent to 1,0 g ceftriaxone.

CEPHTRIFECT 2 000: Each vial contains dry, sterile ceftriaxone sodium equivalent to 2,0 g ceftriaxone.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

0,5 g powder for solution for injection

1,0 g powder for solution for injection

2,0 g powder for solution for injection

White to light-yellow powder.

On reconstitution, a yellowish to brown-yellow clear solution is obtained.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CEPHTRIFECT is indicated for the treatment of the following infections:

Bacterial septicaemia caused by:

Methicillin-sensitive *Staphylococcus aureus (MSSA), Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli* or *Klebsiella pneumoniae.*

Meningitis caused by:

Haemophilus influenzae, Neisseria meningitides, or *Streptococcus pneumoniae.*

Intra-abdominal infections caused by:

Escherichia coli, Klebsiella pneumoniae, or *Peptostreptococcus* species.

Skin and skin structure infections caused by:

Methicillin-sensitive *Staphylococcus aureus (MSSA), Streptococcus pyogenes, Streptococcus viridans group, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Serratia marcescens,* or *Peptostreptococcus* species.

Bone and joint infections caused by:

Methicillin-sensitive *Staphylococcus aureus (MSSA), Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae,* or *Enterobacter* species.

Renal and urinary tract infections (complicated and uncomplicated) caused by:

Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii, or *Klebsiella pneumoniae.*

Respiratory tract infections caused by:

Streptococcus pneumoniae, Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis,* or *Serratia marcescens.*

Ear, nose and throat infections (acute bacterial otitis media) caused by:

Streptococcus pneumoniae, Haemophilus influenzae, (including beta-lactamase-producing strains), or *Moraxella catarrhalis* (including beta-lactamase-producing strains).

Uncomplicated gonorrhoea (cervical/urethral and rectal) caused by:

Neisseria gonorrhoeae, including both beta-lactamase-, and non-beta-lactamase-producing strains, and pharyngeal gonorrhoea caused by non-beta-lactamase-producing strains of *Neisseria gonorrhoeae.*

Peri-operative infection prophylaxis.

4.2 Posology and method of administration

Posology

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution to reconstitute CEPHTRIFECT vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.

Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

CEPHTRIFECT and calcium-containing infusions such as parental nutrition should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different infusion times at different sites (see section 4.3, 4.4 and 6.2).

Standard dosage:

Adults and children over 12 years:

The usual dosage is 1 to 2 g CEPHTRIFECT once daily. In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Special dosage instructions:

Meningitis:

In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dose can be adapted accordingly. For bacterial meningitis in adults, the recommended dose is 4 g once daily.

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (both beta-lactamase-producing and non-beta-lactamase-producing strains), a single intramuscular (IM) dose of 250 mg CEPHTRIFECT is recommended.

Peri-operative infection prophylaxis:

A single dose of 1 to 2 g CEPHTRIFECT administered 30 to 90 minutes prior to surgery. In colorectal surgery, administration of CEPHTRIFECT with or without a 5-nitroimidazole, e.g. metronidazole, has been proven effective (separate administration: see “Method of administration”).

Duration of therapy:

The duration of therapy varies according to the course of the disease. Administration of CEPHTRIFECT should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Special populations

Elderly patients:

No dose modification is needed in the elderly.

Impaired renal and hepatic function:

In patients with impaired renal function, there is no need to reduce the dosage of CEPHTRIFECT provided that hepatic function is intact.

In cases of severe renal failure (creatinine clearance < 10 ml/min) the CEPHTRIFECT dosage should not exceed 2 g daily.

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal function is intact.

Paediatric population

Neonates, infants and children up to 12 years:

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days):

20 to 50 mg/kg body weight once daily. The daily dose should not exceed 50 mg/kg.

CEPHTRIFECT is contraindicated in premature neonates up to a corrected age of 41 weeks (gestational age + chronological age) (see section 4.3). CEPHTRIFECT is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see sections 4.3, 4.4 and 4.8).

Infants and children (15 days to 12 years):

20 to 80 mg/kg once daily. For children with bodyweights of 50 kg or more, the usual adult dose should be used. Intravenous doses of ≥ 50 mg/kg body weight should be given by infusion over at least 30 minutes.

Method of administration:

For intravenous, intramuscular or intravenous infusion use.

CEPHTRIFECT must be reconstituted prior to use. Reconstituted solutions retain their physical and chemical stability for 24 hours when kept below 25 °C or 48 hours in the refrigerator at 2 to 8 °C. As a general rule, however, the solutions should be used immediately after preparation. The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the medicine.

For instructions on reconstitution of the medicine 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 medicine (penicillins, monobactams and carbapenems).
- Hyperbilirubinemic neonates, especially prematures, should not be treated with CEPHTRIFECT. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in the patients.

CEPHTRIFECT is contraindicated in:

- Premature neonates up to a corrected age of 41 weeks (gestational age + chronological age).
- Full-term neonates (up to 28 days of age) with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.

– neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4 and 4.8).

Contraindications of lignocaine must be excluded before intramuscular injection of CEPHTRIFECT when lignocaine is used as solvent.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial medicines, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). In case of severe hypersensitivity reactions, treatment with CEPHTRIFECT 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 as contained in CEPHTRIFECT, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if CEPHTRIFECT is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

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, CEPHTRIFECT 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, CEPHTRIFECT 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 CEPHTRIFECT 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 CEPHTRIFECT 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.

CEPHTRIFECT 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 as contained in CEPHTRIFECT (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during ceftriaxone as contained in CEPHTRIFECT treatment in both adults and children.

If a patient develops anaemia while on CEPHTRIFECT, the diagnosis of a cephalosporin-associated anaemia should be considered and CEPHTRIFECT 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 medicine-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial medicines, 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 CEPHTRIFECT and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

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

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 CEPHTRIFECT may lead to false-positive test results.

CEPHTRIFECT 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 CEPHTRIFECT 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.

Antibacterial spectrum

Ceftriaxone as contained in CEPHTRIFECT has a limited spectrum of antibacterial activity and may not be suitable for use as a single medicine 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 professional information 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 CEPHTRIFECT therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of CEPHTRIFECT 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 as contained in CEPHTRIFECT (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 CEPHTRIFECT-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of CEPHTRIFECT (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 CEPHTRIFECT 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 CEPHTRIFECT (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If CEPHTRIFECT - associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of CEPHTRIFECT should be considered.

4.5 Interaction with other medicines and other forms of interaction

Interactions of CEPHTRIFECT with calcium containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute CEPHTRIFECT vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when CEPHTRIFECT is mixed with calcium-containing solutions in the same intravenous administration line. CEPHTRIFECT 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, CEPHTRIFECT 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 medicine adjusted accordingly, both during and after treatment with CEPHTRIFECT (see section 4.8).

Renal function impairment has not been observed after concurrent administration of large doses of CEPHTRIFECT and potent diuretics (e.g. furosemide). There is no evidence that CEPHTRIFECT increases renal toxicity of aminoglycosides.

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 CEPHTRIFECT and oral calcium-containing products or interaction between intramuscular CEPHTRIFECT and calcium-containing products (intravenous or oral).

Interaction with laboratory tests:

In patients treated with CEPHTRIFECT the Coombs test and tests for galactosaemia may in rare cases be false-positive.

Non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, glucose level determination in urine during therapy with CEPHTRIFECT should be carried out enzymatically.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of CEPHTRIFECT.

CEPHTRIFECT does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and CEPHTRIFECT.

The elimination of CEPHTRIFECT is not altered by probenecid.

CEPHTRIFECT may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established. CEPHTRIFECT crosses the placental barrier.

Breastfeeding

CEPHTRIFECT is excreted into human milk in low concentrations. Caution is advised in nursing mothers.

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

Since CEPHTRIFECT sometimes induces dizziness, the ability to drive and use machines can be impaired (see section 4.8). Patients should be cautious when driving or operating machinery.

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4.8 Undesirable effects

Tabulated summary of adverse reactions

Infections and infestations:	
Less frequent:	Genital fungal infection, Pseudo-membranous colitis[b].
Frequency unknown[a]:	Superinfection[b].
Blood and lymphatic system disorders:	

Frequent:	Eosinophilia, leucophilia, thrombocytopenia.
Less frequent:	Granulocytopenia, anaemia, coagulopathy.
Frequency unknown[a]:	Haemolytic anaemia[b], agranulocytosis.
Immune system disorders:	
Frequency unknown[a]:	Anaphylactic shock, anaphylactoid reaction, hypersensitivity[b], Jarisch-Herxheimer reaction[b].
Nervous system disorders:	
Less frequent:	Headache, dizziness, encephalopathy.
Frequency unknown[a]:	Convulsions.
Ear and labyrinth disorders:	
Frequency unknown[a]:	Vertigo.
Cardiac disorders:	
Frequency unknown:	Kounis syndrome.
Respiratory, thoracic and mediastinal disorders:	
Less frequent:	Bronchospasm.
Gastrointestinal disorders:	
Frequent:	Loose stools/diarrhoea.
Less frequent:	Nausea, vomiting.
Frequency unknown[a]:	Pancreatitis, stomatitis, glossitis, pseudomembranous colitis.
Hepatobiliary disorders:	
Frequent:	Increased hepatic enzymes.
Frequency unknown[a]:	Gall bladder precipitation[b], kernicterus, hepatotoxicity.
Skin and subcutaneous tissue disorders:	
Frequent:	Rash.
Less frequent:	Urticaria, exanthema, allergic dermatitis, pruritus, oedema.
Frequency unknown[a]:	Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome[b] or Lyell's syndrome/toxic epidermal necrolysis[b], acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS)[b]) have been reported, linear IgA disease.
Renal and urinary disorders:	
Less frequent:	Genital mycosis, haematuria, glycosuria.
Frequency unknown[a]:	Oliguria, renal precipitation (reversible).
General disorders and administration site conditions:	
Less frequent:	Phlebitis, injection site pain, pyrexia, oedema, chills.
Phlebitic reactions may occur after IV administration. These may be minimised by slow (2 to 4 minutes) injection of the medicine. Intramuscular injection without lignocaine solution is painful (see section 4.2).	
Investigations:	
Less frequent:	Fever, increase in serum creatinine, shivering.
Frequency unknown[a]:	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 frequency unknown.

[b] See section 4.4

CEPHTRIFECT must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines.

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 post renal 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 to 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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In the case of overdosage nausea, vomiting, diarrhoea, can occur. CEPHTRIFECT concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 20.1.1 Broad and medium spectrum antibiotics

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

Mechanism of action

Ceftriaxone is a third generation cephalosporin. The bactericidal activity of ceftriaxone results from inhibition of 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.

5.2 Pharmacokinetic properties

Absorption:

The maximum concentration after a single intramuscular (IM) dose of 1,0 g is about 81 mg/l and is reached within 2 to 3 hours after administration.

The area under the plasma concentration versus time curve (AUC) after intramuscular (IM) administration is equivalent to that after intravenous (IV) administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly administered ceftriaxone.

Distribution:

The apparent volume of distribution of ceftriaxone is 0,13 to 0,19 l/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1 to 2 g; concentrations well above the minimum inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in body-fluids or tissues including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

Protein binding:

Ceftriaxone is reversibly bound to albumin. There is proportionally decreased albumin binding with an increase in plasma concentration of ceftriaxone.

Penetration into particular tissues:

Paediatrics:

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations exceed 1,4 mg/l in the cerebrospinal fluid (CSF) 24 hours after IV injection in doses of 50 mg/kg in neonates to 100 mg/kg in infants. Peak concentration in CSF with a mean of 18 mg/l is reached about 4 hours after intravenous injection.

Mean CSF concentrations are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis.

The mean values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in paediatric patients suffering from bacterial meningitis are shown in the table below.

Mean pharmacokinetic parameters of ceftriaxone in paediatric patients with meningitis:

	50 mg/kg IV	***75 mg/kg IV***
Maximum plasma concentrations (µg/ml)	216	275
Elimination half-life (h)	4,6	4,3
Plasma clearance (ml/h/kg)	49	60
Volume of distribution (ml/kg)	338	373
CSF concentration – inflamed meninges (µg/ml)	5,6	6,4
Range (µg/ml)	1,3 to 18,5	1,3 to 44
Time after dose (h)	3,7 (± 1,6)	3,3 (± 1,4)

Adults:

In meningitis in adults, administration of 50 mg/kg leads within 2 to 24 hours to CSF concentrations several times higher than the minimum *in vitro* inhibitory concentrations required for the most common meningitis pathogens.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk in low concentrations.

In healthy, young adult volunteers the total plasma clearance is 10 to 22 ml/min.

The renal clearance is 5 to 12 ml/min. 50 to 60 % of ceftriaxone is excreted unchanged in the urine, while 40 to 50 % is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special clinical situations:

Neonates:

Urinary recovery accounts for about 70 % of the dose.

Infants less than eight days old and elderly persons aged over 75 years:

Elimination half-life is usually 2 to 3 times that in young adults.

Patients with renal or hepatic dysfunction:

The pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased.

Impaired kidney function alone:

Biliary elimination of ceftriaxone is increased.

Impaired liver function alone:

Renal elimination of ceftriaxone is increased.

Micro-organisms resistant to ceftriaxone:

Methicillin-resistant *Staphylococcus* species*; Enterococcus faecum; Listeria monocytogenes; Pseudomonas aeruginosa; Ureaplasma urealyticum; Mycoplasma* species*; Mycobacterium* species; some isolates of *Bacteroides* species (bile sensitive); and most strains of *Clostridium difficile.*

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

CEPHTRIFECT should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when CEPHTRIFECT is mixed with calcium-containing solutions in the same IV administration line. CEPHTRIFECT must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, CEPHTRIFECT 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.

6.3 Shelf life

Unopened - 36 months

The reconstituted solution is intended for immediate use, but the solution may be stored in the original vials in the refrigerator at 2 to 8 °C for 48 hours or below 25 °C for 24 hours.

After use, discard any remaining solution.

6.4 Special precautions for storage

Store in the original packaging (in the outer carton) at or below 25 °C and protect the vials from light.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

CEPHTRIFECT 500 powder for solution for injection:

White to yellowish powder in a 15 ml injection vial made of colourless glass, with a rubber stopper and aluminium cap with a colourless flip-off plastic cap.

CEPHTRIFECT 1 000 powder for solution for injection:

White to yellowish powder in a 15 ml injection vial made of colourless glass, with a rubber stopper and aluminium cap with a colourless flip-off plastic cap.

CEPHTRIFECT 2 000 powder for solution for injection:

White to yellowish powder in a 30 ml injection vial made of colourless glass, with a rubber stopper and aluminium cap with a colourless flip-off plastic cap.

On reconstitution, a yellowish to brown-yellow clear solution is obtained.

Packs for IM, IV or IV infusion containing:

CEPHTRIFECT 500, 1 000 and 2 000 Powder for solution for injection is packed in cartons containing 1 or 10 single dose colourless glass vial/s with a rubber stopper and aluminium cap with a colourless flip-off plastic cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

CEPHTRIFECT is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Intramuscular injection:

For IM injection, CEPHTRIFECT 1 000 is dissolved in 3,5 ml of water for injection.

Intramuscular administrations of some cephalosporins cause pain at the injection site. This can be reduced greatly by administering in combination with a local anaesthetic.

CEPHTRIFECT dissolved in 3,5 ml of a 1 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 g be injected at one site.

Reconstitution with 1 % lignocaine (without adrenaline) has no effect on the absorption or the elimination of CEPHTRIFECT.

In case lignocaine is used as a solvent, CEPHTRIFECT solutions should only be used for intramuscular injection

The lignocaine solution must never be administered intravenously.

Intravenous injection:

For IV injection CEPHTRIFECT 500 is dissolved in 5 ml, and CEPHTRIFECT 1 000 in 10 ml, sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

Intravenous infusion:

The infusion should be given over a period of at least 30 minutes.

For IV infusion, 2 g CEPHTRIFECT is dissolved in approximately 40 ml of one of the following calcium-free infusion solutions:

- Sodium chloride 0,9 %.
- Sodium chloride 0,45 % + dextrose 2,5 %.
- Dextrose 5 %.
- Dextrose 10 %.
- Dextran 6 % in dextrose 5 %.
- Hydroxy ethyl starch 6 to 10 % infusions.
- Sterile water for injection.

CEPHTRIFECT should not be mixed with or piggybacked into solutions containing other antimicrobial medicines or into diluent solutions other than those listed above, owing to possible incompatibility.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBERS

CEPHTRIFECT 500: 41/20.1.1/0866

CEPHTRIFECT 1 000: 41/20.1.1/0867

CEPHTRIFECT 2 000: 41/20.1.1/0868

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2008.

10 DATE OF REVISION OF THE TEXT

14 February 2025

iPharma