Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KOCEF-250 (INJECTION)

KOCEF-500 (INJECTION)

KOCEF-1000 (INJECTION)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KOCEF-250

Each vial contains ceftriaxone sodium equivalent to 250 mg ceftriaxone.

Each vial contains approximately 20,75 mg of sodium.

Sugar free.

KOCEF-500

Each vial contains ceftriaxone sodium equivalent to 500 mg ceftriaxone.

Each vial contains approximately 41,5 mg of sodium.

Sugar free.

KOCEF-1000

Each vial contains ceftriaxone sodium equivalent to 1000 mg ceftriaxone.

Each vial contains approximately 83 mg of sodium.

Sugar free.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Sterile, white to yellowish-orange powder in clear glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KOCEF is indicated for the treatment of the following infections when caused by susceptible organisms:

Bacterial septicaemia caused by:

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

Meningitis caused by:

Haemophilus influenzae, Neisseria meningitidis, or Streptococcus pneumoniae.

Intra-abdominal infections caused by:

Escherichia coli, Klebsiella pneumonia, Clostridium species (Note: most strains of Clostridium difficile are resistant) 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, Pseudomonas aeruginosa, 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 penicillinase, and non-penicillinase-producing strains, and pharyngeal gonorrhoea caused by non-penicillinase-producing strains of *Neisseria gonorrhoeae*.

Surgical prophylaxis: The pre-operative administration of a single 1 g dose of KOCEF may reduce the incidence of post-operative infections.

4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years.

The usual dosage is 1 – 2 g KOCEF once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage

may be raised to 4 g, once daily.

Refer below to “Special dosage instructions” for other patient populations.

Duration of treatment

The duration of treatment varies according to the course of the disease. Administration of KOCEF 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.

Combination treatment

Synergy between KOCEF and aminoglycosides has been demonstrated with many Gram- negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Due to chemical incompatibility between KOCEF and aminoglycosides, the two medicines must be administered separately at the recommended dosages.

Chemical incompatibility with KOCEF has also been observed with IV administration of amsacrine, vancomycin and fluconazole.

Special dosage instructions

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 – 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. KOCEF is contraindicated in premature neonates up to corrected age of 41 weeks (gestational age + chronological age) (see section 4.3). KOCEF 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).

For neonates, infants and children (15 days to 12 years):
20 – 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 bodyweight in infants and children up to 12 years of age should be given by infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Meningitis

In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (up to a maximum of 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dose can be adapted accordingly.

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

Elderly population

No dose adjustment of KOCEF is required in patients ≥ 65 years of age provided there is no severe renal and hepatic impairment.

Hepatic impairment

No dose adjustment is required, provided renal function is not impaired.

Renal impairment

In patients with impaired renal function there is no need to reduce the dosage of KOCEF, provided hepatic function is not impaired. In cases of severe renal failure (creatinine clearance < 10 mL/min) the KOCEF dosage should not exceed 2 g daily.

Dialysis

KOCEF is not removed by peritoneal- or hemo- dialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should however be monitored, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Severe renal and hepatic impairment

In patients with both severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary, the dose should be adjusted.

Clinical monitoring for safety and efficacy is advised in these patients.

Meningitis

For bacterial meningitis in *adults*, the recommended dose is 4 g daily.

For dosages recommended in children see section “Paediatric population: Meningitis” above.

Lyme borreliosis

50 mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.

Gonorrhoea

In the treatment of uncomplicated gonorrhoea (penicillinase-producing and non-penicillinase-producing strains) a single IM dose of 250 mg is recommended.

Peri-operative infection prophylaxis

A single dose of 1 to 2 g, depending on the risk of infection, 30 to 90 minutes prior to surgery. In colorectal surgery, administration of KOCEF with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, see “Method of administration” below) has been proven effective.

Method of administration

Ceftriaxone must be reconstituted prior to use and can be administered by intramuscular or intravenous injection. As a general rule 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 dilution of the product before administration, see section 6.6.

For storage instructions after dilution, see section 6.3.

If the solvent used for dilution is lidocaine (lignocaine), this solution must never be administered intravenously (see section 4.3).

Incompatibilities

See section 6.2.

4.3 Contraindications

- Hypersensitivity: known hypersensitivity to ceftriaxone or to any other cephalosporins. Patients with previous hypersensitivity reactions to penicillin and other beta lactam medicines may be at greater risk of hypersensitivity to ceftriaxone (see section 4.4).
- Lidocaine/lignocaine: contraindications to lidocaine/lignocaine must be excluded before intramuscular injection of KOCEF when lidocaine/lignocaine solution is used as a solvent (see section 4.2). See the contraindications section in the professional information of lidocaine. KOCEF solutions containing lidocaine (lignocaine) should never be administered intravenously.
- Premature neonates: KOCEF is contraindicated in premature neonates up to adjusted age of 41 weeks (gestational age + chronological age).
- Hyperbilirubinemic newborns: hyperbilirubinaemic newborns, should not be treated with KOCEF. *In vitro* studies have shown that KOCEF can displace bilirubin from its binding to serum albumin leading to a possible risk of bilirubin encephalopathy in these patients.

- Neonates and calcium containing IV solutions: KOCEF 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. A small number of cases of fatal outcomes with calcium-ceftriaxone precipitates in the lungs and kidneys have been reported at autopsy in both term and preterm neonates receiving KOCEF and calcium- containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate to whom KOCEF and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see sections 4.2, 4.4 and 4.8).

4.4 Special warnings and precautions for use

Interaction with calcium containing products

KOCEF must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. KOCEF and IV calcium-containing solutions or products must not be administered within 48 hours of each other.

Precipitation of ceftriaxone-calcium may occur when KOCEF is mixed with calcium-containing solutions in the same IV administration line. KOCEF must

not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. Fatal outcomes have been reported in neonates receiving KOCEF and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both KOCEF and calcium- containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom KOCEF and calcium-containing fluids were administered at different time points via different intravenous lines. In some cases times of administration of ceftriaxone and calcium-containing solutions differed (see sections 4.2, 4.3, 4,5 and 4.8).
Do not use diluents containing calcium, such as Ringer's lactate solution or Hartmann's solution to reconstitute KOCEF. Precipitate formation can result.

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, KOCEF and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patients irrespective of age even via different infusion lines at different sites.
As a further theoretical consideration and based on 5 half-lives of ceftriaxone, KOCEF and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see sections 4.2, 4.3, 4.5 and 4.8).
No data are available on potential interaction between KOCEF and oral calcium-containing products or interaction between intramuscular KOCEF and calcium-containing products (IV or oral).

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with KOCEF 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 KOCEF 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).

Paediatric population

Safety and effectiveness of KOCEF in neonates, infants and children have been established for the dosages described under section 4.2. Studies have shown that KOCEF, like some other cephalosporins, can displace bilirubin from serum albumin.

KOCEF is contraindicated in neonates (especially prematures) 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 KOCEF (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during KOCEF 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.

Use of lidocaine (lignocaine)

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

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of KOCEF, and may range in severity from mild diarrhoea to fatal colitis. Treatment with KOCEF alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Toxin hyperproducing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following KOCEF use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of

antibacterial medicines, such as KOCEF.

If CDAD is suspected or confirmed, on-going antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Superinfections

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 KOCEF may lead to false-positive test results. KOCEF 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 KOCEF 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 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.

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. Precipitates of calcium ceftriaxone have been occasionally associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the medical practitioner based on specific benefit risk assessment (see section 4.8).

Biliary stasis/ Pancreatitis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with KOCEF (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 KOCEF-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 medical doctor based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

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

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone, such as in KOCEF (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 KOCEF should be considered.

Long term treatment: Blood monitoring

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

Special groups

Patients with reduced renal and liver function: Refer to section 4.2.

The elderly: Refer to section 4.2.

Children: Refer to section 4.2.

Excipient sodium

Each KOCEF 250 mg vial contains less than 1 mmol sodium (23 mg) per 250 mg vial, i.e. is essentially “sodium free”.

Each KOCEF 500 mg vial contains approximately 41,5 mg of sodium per 500 mg vial, equivalent to 2,08 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each KOCEF 1000 mg vial contains approximately 83 mg of sodium per 1 g vial, equivalent to 4,15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Interaction with calcium-containing products

KOCEF should not be added to solutions containing calcium.

Do not use diluents containing calcium such as Ringer’s lactate solution or Hartmann’s solution to reconstitute KOCEF vials, or to further dilute a reconstituted vial for IV administration because a precipitate can form (see sections 4.3, 4.4 and 6.2).

Precipitation of ceftriaxone-calcium can also occur when KOCEF is mixed with calcium-containing solutions in the same IV administration. line. KOCEF must not be administered simultaneously with calcium containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition

via a Y-site (see sections 4.3, 4.4 and 4.8).

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).

Anticoagulants

Concomitant use of KOCEF with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with KOCEF (see section 4.8).

Aminoglycosides

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

Laboratory tests

In patients treated with **KOCEF** the Coombs' test and tests for galactosaemia may become false-positive.

Non-enzymatic methods for glucose determination in urine may give false-positive results.

For this reason, urine-glucose determination during therapy with KOCEF should be done enzymatically.

The presence of KOCEF 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.

Chloramphenicol

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

The clinical relevance of this finding is unknown.

Probenecid

The elimination of **KOCEF** is not altered by probenecid.

Diuretics

Renal function impairment has not been observed after concurrent administration of **KOCEF** and diuretics (e.g. furosemide).

Alcohol

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

KOCEF does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity, birth or perinatal and postnatal development. In

primates, no embryotoxicity or teratogenicity has been observed.

Breastfeeding

Low concentrations of ceftriaxone is excreted in human breast milk.

Caution should be exercised when KOCEF is administered to a breastfeeding woman.

Fertility

Reproductive studies in animals 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 KOCEF, 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

a) Summary of the safety profile

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

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with ceftriaxone.

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known[a]**
Infections and infestations		Genital fungal infection, pseudo-membranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia, leucopenia, thrombocytopenia	Granulocytopenia, anaemia, coagulopathy	Haemolytic anaemia[b], agranulocytosis
Immune system disorders			Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity[b], Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache, dizziness, encephalopathy	Convulsion
Ear and			Vertigo

labyrinth disorders			
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastrointestinal disorders	Diarrhoea, 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 pain, pyrexia, oedema, chills	
Investigations		Blood creatinine increased	Coombs test false positive[b], galactosaemia test false positive, 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

c. Description of selected adverse reactions

Interaction with calcium

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 KOCEF.

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).

Blood and lymphatic system disorders

Isolated cases of agranulocytosis (< 500/mm^3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more. Coagulation disorders have been reported.

Renal and urinary disorders

Renal precipitation has been reported, mostly in children older than 3 years who have been treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding 10 g and presenting with other risk factors (e.g. fluid restrictions, confinement to bed). This event may be symptomatic or asymptomatic, may lead to renal insufficiency, and is reversible upon discontinuation of KOCEF.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via

medsafety@austell.co.za

4.9 Overdose

In the case of overdosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1: Broad and medium spectrum antibiotics.]

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins.

ATC Code: J01DD04

Mechanism of action

The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis.

Ceftriaxone exerts *in vitro* activity against a wide range Gram-negative and Gram-positive micro-organisms. Ceftriaxone is stable to most β-lactamases,

both penicillinases and cephalosporinases, of Gram-positive and Gram-negative bacteria.

Gram positive aerobes

Methicillin-resistant *Staphylococcus* spp. is resistant to ceftriaxone.

Enterococcus faecalis, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram negative aerobes

Some isolates of *Acinetobacter anitratus* (mostly *A.. baumanii*), *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter* spp (other), *Proteus penneri*, *Proteus vulgaris*.

Pseudomonas fluorescens, *Pseudomonas* spp. (other), *Providentia rettgeri*, *Serratia marcescens*, *Serratia* spp. (other) are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.

Some isolates of *Klebsiella pneumoniae* are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase.

Clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Stenotrophomonas maltophilia is inherently resistant.

Anaerobic organisms

Some isolates of *Bacteroides* spp. (bile-sensitive) are resistant to ceftriaxone due to ß-lactamase-production.

Many strains of ß-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant.

Clostridium difficile is resistant.

The WHO Antimicrobial Resistance, Global Report on Surveillance, 2014, lists the following bacteria-antibacterial medicine resistant combinations ranging between 56 % - 90 % for 3rd generation cephalosporins including ceftriaxone as:

E. coli and *K. pneumoniae* mainly conferred by extended spectrum beta-lactamases (ESBLs), and *N. gonorrhoeae*.

Other organisms

Ureaplasma urealyticum, *Mycoplasma* spp., *Mycobacterium* spp., *Chlamydia* spp., *Chlamydophila* spp., *Legionella* spp. and fungi are resistant to ceftriaxone.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total medicine 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.

Absorption

The maximum plasma concentration after a single IM dose of 1,0 g is about 81 mg/L and is reached within 2 - 3 hours after administration. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly administered ceftriaxone.

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean

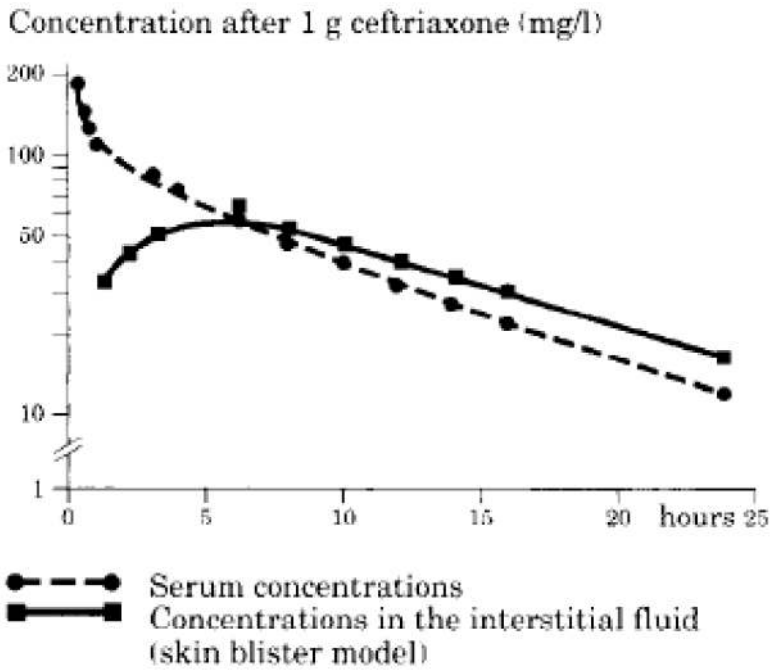
peak plasma ceftriaxone levels are approximately 120 and 200 mg/L respectively. After intravenous infusion of ceftriaxone 500 mg and 1 g, the plasma ceftriaxone levels are approximately 80 and 150 mg/L respectively. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7 - 12 L. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1 - 2 g; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection, are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsils, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

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).



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. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

Biotransformation

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

Elimination

Total plasma clearance is 10 - 22 mL/min. Renal clearance is 5 - 12 mL/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, while 40 - 50 % is excreted unchanged in the bile.

The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special populations

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.

Elderly

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

Renal or hepatic impairment

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

The 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

KOCEF and calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites as it can cause the formation of intravascular precipitates.

KOCEF should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution. Ceftriaxone is incompatible with vancomycin, fluconazole and aminoglycosides.

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

6.3 Shelf life

Unopened vials: 24 months.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature or 24 hours in the refrigerator 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 should not be longer than the times stated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Storage directions for reconstituted product:

Store for up to 6 hours at 25 °C or 24 hours at 2 – 8 °C.

Do not freeze the reconstituted product.

6.5 Nature and contents of container

KOCEF-250: 10 mL clear glass vial with grey bromo butyl stopper and aluminium flip off seal with green plastic top, containing powder equivalent to 250 mg ceftriaxone for reconstitution. Vials are supplied in cartons containing singles.

KOCEF-500: 10 mL clear glass vial with grey bromo butyl stopper and aluminium flip off seal with light blue plastic top, containing powder equivalent to 500 mg ceftriaxone for reconstitution. Vials are supplied in cartons containing singles.

KOCEF-1000: 15 mL clear glass vial with grey bromo butyl stopper and aluminium flip off seal with grey plastic top, containing powder equivalent to 1 g ceftriaxone for reconstitution.

Vials are supplied in cartons containing singles.

6.6 Special precautions for disposal and other handling

Intramuscular injection

For intramuscular injection, KOCEF 250 mg or 500 mg is dissolved in 2 mL and KOCEF 1 g in 3,5 mL, of water for injection. In adults, intramuscular administrations of some cephalosporins, including KOCEF, cause pain at the injection site. This can be reduced greatly by administering in combination with a local anaesthetic.

KOCEF dissolved in 3,5 mL of a 1 % lidocaine (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. Safe dose of 1 % lidocaine (lignocaine) has not been established.

Reconstitution with 1 % lidocaine / lignocaine (without adrenaline/ epinephrine) has no effect on the absorption or the elimination of KOCEF.

The lidocaine (lignocaine) solution must never be administered intravenously (see section 4.3).

Intravenous injection

For intravenous injection, KOCEF 250 mg or 500 mg is dissolved in 5 mL, and KOCEF 1 g in 10 mL sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

7. HOLDER OF CERTIFICATE OF REGISTRATION

DEZZO TRADING 392 (PTY) LTD

Cnr Birch & Bluegum Avenue,

Anchorville,

Lenasia,

1827

8. REGISTRATION NUMBER(S)

KOCEF-250: A38/20.1.1/0553

KOCEF-500: A38/20.1.1/0554

KOCEF-1000: A38/20.1.1/0555

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2005

10. DATE OF REVISION OF THE TEXT

22 March 2023