PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

OBKEF 250 mg INJECTION Powder for Injection

OBKEF 500 mg INJECTION Powder for Injection

OBKEF 1 g INJECTION Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

OBKEF 250 mg INJECTION powder for injection:

Each vial contains Ceftriaxone sodium equivalent to Ceftriaxone 250 mg.

OBKEF 500 mg INJECTION powder for injection:

Each vial contains Ceftriaxone sodium equivalent to Ceftriaxone 500 mg.

OBKEF 1 g INJECTION powder for injection:

Each vial contains Ceftriaxone sodium equivalent to Ceftriaxone 1 g.

OBKEF contains approximately 83 mg (3.6 mmol) of sodium per gram of ceftriaxone.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Injection

OBKEF 250 mg INJECTION powder for injection: A white to yellowish crystalline powder.

OBKEF 500 mg INJECTION powder for injection: A white to yellowish crystalline powder.

OBKEF 1 g INJECTION powder for injection: A white to yellowish crystalline powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

OBKEF 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, Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae.*
- **Meningitis** caused by *Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumonia.*
- **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 pneumonia.*
- **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 pneumonia, Haemophilus influenzae* (including beta-lactamase producing strains), or *Moraxella catarrhalis* (including beta-lactamase producing strains).
- **Uncomplicated gonorrhoea** *(cervical/urethral and rectal)* caused by *Neisseria gonorrhoea* 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 OBKEF may reduce the incidence of post-operative infections.

4.2 Posology and method of administration

Posology

Standard dosage

***Adults and children over twelve years*:**

The usual dosage is 1 to 2 g of OBKEF *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.

***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. It is not necessary to differentiate between premature and term infants.

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.

Duration of therapy

The duration of therapy varies according to the course of the disease. Administration of OBKEF 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 dosage instructions

***Meningitis*:** In bacterial meningitis in neonates, infants and children, treatment begins with doses of 100 mg per kg (not exceeding 4 g), once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. For bacterial meningitis in adults, the recommended dose is 4 g daily.

***Gonorrhoea*:** For the treatment of uncomplicated gonorrhoea (penicillinase-producing and non-penicillinase-producing strains), a single IM dose of 125 mg OBKEF is indicated.

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

Special populations

Elderly patients:

The dosages recommended for adults require no modification in the case of elderly patients.

Impaired renal and hepatic function:

In patients with hepatic damage, the dosage need not be reduced if renal function is intact.

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

Method of administration

OBKEF must be reconstituted prior to use. For instructions on reconstitution of OBKEF before administration, see section 6.6. Calcium containing solutions are not among appropriate solutions described for reconstitution, due to incompatibility (see section 6.2).

Intramuscular injection:

OBKEF can be administered by deep intramuscular injection. OBKEF must be injected well within the bulk of a relatively large muscle. It is recommended that not more than 1 g be injected at one site. As the solvent used is lidocaine (lignocaine) the resulting solution must never be administered intravenously (see section 4.3).

***Intravenous injection*:** OBKEF can be administered by slow intravenous injection. The intravenous administration should be given over 2 to 4 minutes.F

***Intravenous infusion*:**

OBKEF can be administered by intravenous infusion. The infusion should be given over a period of at least 30 minutes (preferred route).

4.3 Contraindications

Hypersensitivity to ceftriaxone or to any other cephalosporin.

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

Safety in pregnancy and lactation has not been established.

It is excreted in breast milk at low concentrations, caution is advised in breastfeeding mothers.

OBKEF is contraindicated in premature neonates, full-term neonates:

- with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients
- if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.8 and 6.2*).*

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

Ceftriaxone solutions containing lidocaine (lignocaine) should never be administered intravenously.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Hypersensitivity reactions

As with all beta-lactam antibacterial medicines, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with OBKEF 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 medicine. Caution should be used if ceftriaxone as in OBKEF is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) 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). When SCAR is suspected OBKEF should be discontinued.

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. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone as in OBKEF 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 as in OBKEF must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2).

Paediatric population

Safety and effectiveness of ceftriaxone as in OBKEF 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.

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

If a patient develops anaemia while on OBKEF, the diagnosis of a cephalosporin-associated anaemia should be considered and OBKEF 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 agents, including ceftriaxone as in OBKEF, 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 OBKEF (see section 4.8). Discontinuation of therapy with ceftriaxone as in OBKEF 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 ceftriaxone as in OBKEF may lead to false-positive test results. OBKEF 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 OBKEF should be done enzymatically (see section 4.8).

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

Sodium

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

Antibacterial spectrum

Ceftriaxone as in OBKEF 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 as in OBKEF, administration of an additional antibiotic should be considered.

Use of lidocaine (lignocaine)

In case a lidocaine (lignocaine) solution is used as a solvent, ceftriaxone as in OBKEF 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.

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 as in OBKEF 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 associated with symptoms in a few cases. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of OBKEF treatment should be considered by the medical practitioner 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 in OBKEF (see section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of ceftriaxone-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone as in OBKEF (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 practitioner based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

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

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute OBKEF vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when OBKEF is mixed with calcium-containing solutions in the same intravenous administration line. OBKEF 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, OBKEF and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. It has been reported that *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 OBKEF (see section 4.8).

There is no evidence that ceftriaxone as in OBKEF increases renal toxicity of aminoglycosides.

It was reported that in an *in-vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

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

In patients treated with ceftriaxone as in OBKEF, the Coombs' test may lead to false-positive test results. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

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

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

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

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

Ceftriaxone as contained in OBKEF does not contain an N-methyl-thiotetrazole moiety associated with possible ethanol intolerance and bleeding problems.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations, caution is advised in breastfeeding 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

OBKEF may cause dizziness which may influence the ability to drive and use machines (see section 4.8). Patients should not drive or operate machines.

4.8 Undesirable effects

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

System Organ Class	Adverse reaction	Frequency
Infections and Infestations	Genital fungal infection Pseudo-membranous colitis	Less frequent
	Superinfection	Not known
Blood and lymphatic system disorders	Eosinophilia, leucopenia, thrombocytopenia	Frequent
	Granulocytopenia, anaemia, coagulopathy, haematoma or bleeding.	Less frequent
	Haemolytic anaemia, agranulocytosis	Not known

Immune system disorders	Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, Jarisch-Herxheimer reaction	Not known
Nervous system disorders	Headache, dizziness	Less frequent
	Convulsion	Not known
Ear and labyrinth disorders	Vertigo	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Less frequent
Gastrointestinal disorders	Diarrhoea, loose stools	Frequent
	Nausea, vomiting	Less frequent
	Pancreatitis, Stomatitis, Glossitis	Not known
Hepato-biliary disorders:	Hepatic enzyme increased	Frequent
	Gall bladder precipitation, Kernicterus	Not known
Skin and subcutaneous tissue disorder	Rash	Frequent
	Pruritus, urticaria, petechiae, purpura, diaphoresis, flushing, allergic dermatitis, exanthema	Less frequent
	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS),	Not known

	exfoliative dermatitis	
Renal and urinary disorders	Haematuria, glycosuria	Less frequent
	Oliguria, renal precipitation (reversible)	Not known
General disorders and administrative site conditions	Phlebitis, injection site pain, pyrexia, Oedema, chills	Less frequent
Investigations	Blood creatinine increased	Less frequent
	Coombs test false positive, galactosaemia test false positive, non enzymatic methods for glucose determination false positive	Not known

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.

4.9 Overdose:

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur, (see section 4.8). Plasma concentrations of ceftriaxone as in OBKEF 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

A 20.1.1 Broad and medium spectrum antibiotics.

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

ATC code: J01DD04

Ceftriaxone is a cephalosporin antibiotic, usually active against a wide range of gram-negative and gram-positive micro-organisms. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone is stable to most β-lactamases, both penicillinases and cephalosporinases of gram-positive and gram-negative bacteria.

Mode of 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 depressed 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.

Resistant Gram-positive organisms:

Methicillin-resistant Staphylococcus spp., *Listeria monocytogenes, Enterococcus faecium and Enterococcus faecalis.*

Resistant Gram-negative organisms:

Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, ESBL producing *Eshericia coli, Klebsiella pneumoniae and Klebsiella oxytoca, Moranella morganii, Proteus vulgaris, Serratia marcescens, Acinotobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia.*

Resistant Anaerobic organisms:

Clostridium spp. (*Clostridium difficile*) is resistant. Many strains of β-lactamase-producing *Bacteroides spp*. (notably *B. fragilis*) are resistant. *Fusobacterium spp*., *Peptostreptococcus spp*.

The following organisms are also resistant: *Chlamydia spp., Chlamydophila spp., Mycoplasma spp., Legionella spp., Ureaplasma urealyticum, Mycobacterium spp*., and fungi.

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 drug concentrations.

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.

Distribution:

The volume of distribution of ceftriaxone is 7 to 12 litres. Ceftriaxone has shown excellent tissue and fluid penetration after a dose of 1 to 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 cerebrospinal, pleural, prostatic and synovial fluids.

On intravenous administration, ceftriaxone diffuses into the interstitial fluid, where if it is given in the recommended dosage range, bactericidal concentrations lasting 24 hours may be maintained.

Protein binding: Ceftriaxone is reversibly bound to albumin and the binding decreases with the increase in concentration, e.g. from 95 % binding at plasma concentrations of < 100 mg/l to 85 % binding at 300 mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Penetration into particular tissues: 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 of OBKEF in doses of 50-100 mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18 mg/l. Mean CSF levels are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis. The average 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:

Average 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 (hr)	4,6	4,3
Plasma Clearance (ml/hr/kg)	49	60
Volume of distribution (ml/kg)	338	373
CSF Concentration – inflamed meninges (µg/ml) Range (µg/ml) Time after dose (hr)	5,6 1,3 – 18,5 3,7 (± 1,6)	6,4 1,3 – 44 3,3 (± 1,4)

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

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

Biotransformation:

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

Elimination:

In healthy, young adult volunteers the total plasma clearance is 10 to 22 ml/min. The renal clearance is 5 - 12 ml/min. 50 to 60 % 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.

Special populations:

In neonates, urinary recovery accounts for 70 % of the dose.

In infants aged less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 to 3 times that in young adults.

Patients with 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. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients used in this formulation.

6.2 Incompatibilities

OBKEF must not be mixed with other medicines or solutions except those mentioned in section 6.6.

OBKEF should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution. Particulate formation can result (see section 4.2 and 4.4).

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

6.3 Shelf life

OBKEF 250 mg INJECTION powder for injection:

Unopened vials: 2 years

OBKEF 500 mg INJECTION powder for injection:

Unopened vials: 2 years

OBKEF 1 g INJECTION powder for injection:

Unopened vials: 3 years

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at ± 5 °C).

As a general rule, the solution should be used immediately after preparation. The solution 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.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicine, see section 6.3.

6.5 Nature and contents of container

OBKEF 250 mg, 500 mg and 1 g powder for injection are packed in USP type II 10 ml flint glass vial stoppered with 20 mm grey bromo butyl rubber stoppers and sealed with 20 mm orange flip-off Aluminium seal. Each vial is placed in a cardboard carton. (1 x Vial).

6.6 Special precautions for disposal and other handling

Intramuscular injection: For IM injection OBKEF 250 mg or 500 mg is dissolved in 2 ml and OBKEF 1 g in 3,5 ml of water for injection. OBKEF dissolved in a 1 % lidocaine (lignocaine) solution instead of water for injection can reduce pain at the site of injection.

Intravenous injection: For IV injection, OBKEF 250 mg or 500 mg is dissolved in 5 ml, and OBKEF 1 g in 10 ml sterile water for injection.

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

Sodium chloride 0,9 %, sodium chloride 0,45 % + dextrose 2,5 %, dextrose 5 %, dextrose 10 %, dextran 6 % in dextrose 5 %, hydroxyethyl-starch 6 – 10 % infusions, sterile water for injection.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

8 REGISTRATION NUMBER(S):

OBKEF 250 mg INJECTION powder for injection: 49/20.1.1/0416

OBKEF 500 mg INJECTION powder for injection: 49/20.1.1/0417

OBKEF 1 g INJECTION powder for injection: 47/20.1.1/1245

9 DATE OF FIRST AUTHORISATION

Date of registration: 17 August 2021

10 DATE OF REVISION OF THE TEXT

Not applicable