PROFESSIONAL INFORMATION

Scheduling status: S4

1. Name of the medicine

CEFTRIAXONE 500 mg FKSA Powder for solution for injection.

CEFTRIAXONE 1 g FKSA Powder for solution for injection.

CEFTRIAXONE 2 g FKSA Powder for solution for infusion.

2. Qualitative and quantitative composition

CEFTRIAXONE 500 mg FKSA powder for solution for IM or IV injection

Each vial contains 500 mg ceftriaxone as ceftriaxone sodium.

CEFTRIAXONE 1 g FKSA powder for solution for IM or IV injection

Each vial contains 1 g ceftriaxone as ceftriaxone sodium.

CEFTRIAXONE 2 g FKSA powder for solution for IV infusion.

Each vial or bottle contains 2 g ceftriaxone as ceftriaxone sodium.

Excipient with known effect:

Contains sodium (approximately 83 mg (3,6 mmol sodium ion) per gram of CEFTRIAXONE FKSA).

The pH of freshly reconstituted solutions usually ranges from 6 to 8.

Sugar free.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

2 g powder for solution for infusion

1 g powder for solution for injection

500 mg powder for solution for injection

Powder for solution for infusion or injection.

White to almost white or yellowish, crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

CEFTRIAXONE FKSA 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* or *Streptococcus pneumoniae.*

Intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, 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 CEFTRIAXONE FKSA may reduce the incidence of post-operative infections.

In the treatment of infections caused by *Pseudomonas aeruginosa,* an aminoglycoside should be administered concomitantly.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

The usual dosage is 1 - 2 g of CEFTRIAXONE FKSA *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 - 80 mg/kg once daily.

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

Intravenous doses of ≥ 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

Elderly patients:

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

Duration of therapy:

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

Special dosage instructions

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 dosage can be reduced accordingly.

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

Gonorrhoea:

In the treatment of uncomplicated gonorrhoea (penicillinase-producing and non-penicillinase-producing strains) a single IM dose of 125 mg is recommended.

Perioperative prophylaxis:

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

Impaired renal and hepatic function

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

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

Method of administration

CEFTRIAXONE FKSA must be reconstituted prior to use.

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, 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.

Intramuscular injection. For *IM* injection, CEFTRIAXONE 500 mg FKSA is dissolved in 2 mL, and CEFTRIAXONE 1 g FKSA in 3,5 mL, of water for injection or 1 % lidocaine (lignocaine) hydrochloride solution (to reduce pain at the site of

injection). CEFTRIAXONE FKSA must be injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site.

Reconstitution with 1 % lidocaine (lignocaine) (without epinephrine (adrenaline)) has no effect on the absorption or the elimination of CEFTRIAXONE FKSA. The lidocaine solution should never be administered intravenously.

Intravenous injection. For *IV* injection, CEFTRIAXONE 500 mg FKSA is dissolved in 5 mL, and CEFTRIAXONE 1 g FKSA 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 at least 30 minutes. For *IV* infusion, CEFTRIAXONE 2 g FKSA is dissolved in 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 6-10 % infusion, sterile water for injection.

CEFTRIAXONE FKSA solutions 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.

Incompatibilities: See section 6.2.

4.3 Contraindications

- Hypersensitivity to ceftriaxone or to any other cephalosporin,.or to any of the excipients of CEFTRIAXONE FKSA 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).

- CEFTRIAXONE FKSA is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) *.
- CEFTRIAXONE FKSA is also contraindicated in full-term neonates (up to 28 days of age):
  - with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*
  - if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a CEFTRIAXONE FKSA calcium salt (see sections 4.4, 4.8 and 6.2).

* CEFTRIAXONE FKSA can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients. See section 4.4.

Contraindications to lidocaine (lignocaine) should be excluded before intramuscular injection of CEFTRIAXONE FKSA when lidocaine (lignocaine) solution is used as a solvent (see section 4.4). See information in the Professional Information of lidocaine (lignocaine), especially contraindications.

CEFTRIAXONE FKSA 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

Serious and occasionally fatal hypersensitivity reactions have been reported with beta-lactam antibiotics (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 CEFTRIAXONE FKSA must be discontinued immediately and adequate emergency measures should be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone as in CEFTRIAXONE FKSA, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if CEFTRIAXONE FKSA 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 (SJS), or Lyell's syndrome/toxic epidermal necrolysis (TEN), “drug reaction with eosinophilia and systemic symptoms” (DRESS) and generalised exanthematous pustulosis (AGEP) which can be life-threatening or fatal have been reported in association with beta-lactam antibiotics such as CEFTRIAXONE FKSA treatment. The frequency of these events is not known (see section 4.8). When SCAR is suspected CEFTRIAXONE FKSA 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. At least one of them had received ceftriaxone as in CEFTRIAXONE FKSA 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 as in CEFTRIAXONE FKSA 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 FKSA must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. See section 4.3.

However, in patients older than 28 days of age CEFTRIAXONE FKSA 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 providers may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of CEFTRIAXONE FKSA is considered necessary in patients requiring continuous nutrition, TPN solutions and CEFTRIAXONE FKSA can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of a TPN solution could be stopped for the period of CEFTRIAXONE FKSA 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 CEFTRIAXONE FKSA 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 as in CEFTRIAXONE FKSA, like some other cephalosporins, can displace bilirubin from serum albumin.

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

If a patient develops anaemia while on CEFTRIAXONE FKSA, the diagnosis of a cephalosporin-associated anaemia should be considered and CEFTRIAXONE FKSA 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 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 FKSA (see section 4.8). Discontinuation of therapy with CEFTRIAXONE FKSA and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Superinfection with non-susceptible microorganisms 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 CEFTRIAXONE FKSA may lead to false-positive test results. Ceftriaxone as in CEFTRIAXONE FKSA 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 CEFTRIAXONE FKSA should be done enzymatically (see section 4.8).

The presence of ceftriaxone as in CEFTRIAXONE FKSA 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 in CEFTRIAXONE FKSA 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 as in CEFTRIAXONE FKSA, 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 CEFTRIAXONE FKSA solutions must only be used for intramuscular injection. Contraindications to lidocaine (lignocaine), warnings and other relevant information as detailed in the product information of lidocaine (lignocaine) should 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 (CEFTRIAXONE FKSA) doses

of 1 g per day and above. Caution should be exercised, particularly in the paediatric population. Such precipitates disappear after discontinuation of CEFTRIAXONE FKSA 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 CEFTRIAXONE FKSA 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 FKSA (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 biliary precipitation related to ceftriaxone 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 practitioner based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

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

Encephalopathy

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

Sodium

CEFTRIAXONE FKSA contains sodium:

- A 500 mg vial contains about 42 mg (1,8 mmol).
- A 1 g vial contains about 83 mg (3,6 mmol).
- A 2 g vial or bottle contains about 166 mg (7,2 mmol).

This should be taken into consideration in patients on a controlled sodium diet.

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 CEFTRIAXONE FKSA vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form.

Precipitation of ceftriaxone-calcium can also occur when CEFTRIAXONE FKSA is mixed with calcium-containing solutions in the same intravenous administration line.

CEFTRIAXONE FKSA must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, CEFTRIAXONE FKSA 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).

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

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 CEFTRIAXONE FKSA (see section 4.8).

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

In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone as in CEFTRIAXONE FKSA.

No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone as in CEFTRIAXONE FKSA 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 ceftriaxone as in CEFTRIAXONE FKSA. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated

with possible ethanol intolerance and bleeding problems. The elimination of CEFTRIAXONE FKSA is not altered by probenecid.

Laboratory tests

In patients treated with ceftriaxone as in CEFTRIAXONE FKSA, the Coombs test may lead to false-positive test results.

Ceftriaxone as in CEFTRIAXONE FKSA, 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 CEFTRIAXONE FKSA should be carried out enzymatically.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established. Ceftriaxone crosses the placental barrier. Adequate data on the use of CEFTRIAXONE FKSA in pregnant women are not available. CEFTRIAXONE FKSA should therefore not be used pregnancy.

Breastfeeding

As ceftriaxone as in CEFTRIAXONE FKSA is excreted in the breast milk at 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

CEFTRIAXONE FKSA may cause dizziness which may influence the ability to drive and use machines (see section 4.8). Patients should not drive or operate machines until they know how CEFTRIAXONE FKSA affects them.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse events

System Organ Class	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, neutropenia, haematoma or bleeding
Immune system disorders			Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction,

System Organ Class	Frequent	Less frequent	Not known [a]
			hypersensitivity[b], Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache, dizziness, encephalopathy	Convulsion
Ear and labyrinth disorders			Vertigo
Cardiac disorders			Kounis syndrome
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b], loose stools	Nausea, vomiting	Pancreatitis[b], stomatitis, glossitis
Hepatobiliary disorders	Hepatic enzyme increased		Gall bladder precipitation[b], kernicterus, hepatitis[c], cholestatic hepatitis [b,c]
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria	Stevens Johnson syndrome[b], toxic epidermal necrolysis[b], erythema multiforme, acute generalised exanthematous

System Organ Class	Frequent	Less frequent	Not known [a]
			pustulosis, DRESS[b], exfoliative dermatitis, petechiae, purpura, diaphoresis, flushing
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	False-positive Coombs test [b], false-positive galactosaemia test [b], false-positive non-enzymatic methods for glucose determination [b]

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

[b] See section 4.4

[c] Usually reversible upon discontinuation of ceftriaxone

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

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 lungs and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic and may lead to ureteric obstruction and postrenal acute renal failure but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone-calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes) (see section 4.2). 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

In overdose, symptoms of nausea, vomiting and diarrhoea can occur.

There is no specific antidote. Plasma concentrations of ceftriaxone as in CEFTRIAXONE FKSA cannot be reduced by haemodialysis or peritoneal dialysis. Treatment of overdose should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

A 20.1.1 - Broad and medium spectrum antibiotics.

Mechanism of action

The bactericidal activity of CEFTRIAXONE FKSA results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. CEFTRIAXONE FKSA is stable to most β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. See section 4.1.

Resistance

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftriaxone in at least some types of infections is questionable.

Species for which acquired resistance may be a problem:

Gram-positive aerobes

Staphylococcus epidermidis[+]

Staphylococcus haemolyticus[+]

Staphylococcus hominis[+]

Gram-negative aerobes

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli [%]

Klebsiella pneumoniae [%]

Klebsiella oxytoca [%]

Morganella morganii

Proteus vulgaris

Serratia marcescens

Anaerobes

Bacteroides spp.

Fusobacterium spp.

Peptostreptococcus spp.

Clostridium perfringens

Inherently resistant organisms:

Gram-positive aerobes

Enterococcus spp.

Listeria monocytogenes

Gram-negative aerobes

Acinetobacter baumannii

Pseudomonas aeruginosa

Stenotrophomonas maltophilia

Anaerobes

Clostridium difficile

Others

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Legionella spp.

Ureaplasma urealyticum

£ All methicillin-resistant staphylococci are resistant to CEFTRIAXONE FKSA.

+ Resistance rates > 50 % in at least one region

% ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

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 % bio-availability of intramuscularly administered ceftriaxone.

Distribution

The volume of distribution of ceftriaxone is 7 - 12 litres. Ceftriaxone is widely distributed in tissue and body fluids. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids.

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. 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). 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 ceftriaxone 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 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)	5,6	6,4
Range (μg/mL)	1,3 - 18,5	1,3 - 44
Time after dose (hr)	3,7 (± 1,6)	3,3 (± 1,4)

In adult meningitis patients, administration of 50 mg/kg leads within 2 - 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

The 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 of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered 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.

Elderly

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

Paediatric population

In neonates, urinary recovery accounts for about 70 % of the dose. In infants aged less than 8 days the average elimination half-life is usually 2 - 3 times that in young adults.

Linearity/non-linearity

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

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Solutions containing CEFTRIAXONE FKSA should not be mixed with or added to other medicines except those mentioned in section 6.6. In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute CEFTRIAXONE FKSA vials or bottles or to further dilute a reconstituted vial or bottle for intravenous administration because a precipitate can form. CEFTRIAXONE FKSA must not be mixed or administered simultaneously with calcium-containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

If treatment with a combination of another antibiotic with CEFTRIAXONE FKSA is intended, administration should not occur in the same syringe or in the same infusion solution.

CEFTRIAXONE FKSA must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials or bottles: 3 years

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 12 hours at 25 °C and for 2 days at 2 - 8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally 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 30 °C; keep vial or bottle 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

CEFTRIAXONE 500 mg FKSA powder for solution for injection

15 mL vial, glass, colourless Type II glass vials closed with rubber stoppers and flip-off caps.

Pack size of 1's, 10's or 25's single dose vials.

Not all pack sizes may be marketed.

CEFTRIAXONE 1 g FKSA powder for solution for injection

15 mL vial, glass, colourless Type II glass vials closed with rubber stoppers and flip-off caps.

Pack size of 1's,10's or 25's single dose vials.

Not all pack sizes may be marketed.

CEFTRIAXONE 2 g FKSA powder for solution for infusion

15 mL vial, glass, colourless Type II glass vials closed with rubber stoppers and flip-off caps.

50 mL colourless Type II glass infusion bottles, closed with rubber stoppers and flip-off caps.

Pack size of 1's or 10's single dose vials or 1x single dose bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

CEFTRIAXONE FKSA must be reconstituted prior to use.

For single use only. See sections 6.3 and 6.4.

Concentrations for the intravenous injection: 100 mg/mL

Concentrations for the intravenous infusion: 50 mg/mL

Concentrations for the intramuscular injection: 250 mg/mL

(Please refer to section 4.2 for further information).

Preparation of solutions for injection and infusion

The use of freshly prepared solutions is recommended. Solutions are light yellow to brownish yellow. For storage conditions of the reconstituted medicinal product, see section 6.3.

CEFTRIAXONE FKSA should not be mixed in the same syringe with any medicine other than 1 % lidocaine (lignocaine) hydrochloride solution (for intramuscular injection only).

The infusion line should be flushed after each administration.

Intramuscular injection.

For IM injection, CEFTRIAXONE 500 mg FKSA is dissolved in 2 mL, and CEFTRIAXONE 1 g FKSA in 3,5 mL, water for injection **or** 1 % lidocaine hydrochloride solution (to reduce pain at the site of injection). CEFTRIAXONE FKSA must be injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site.

Reconstitution with 1 % lidocaine (lignocaine) (without epinephrine (adrenaline)) has no effect on the absorption or the elimination of CEFTRIAXONE FKSA. **The lidocaine (lignocaine) solution should never be administered intravenously**.

Intravenous injection

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

Intravenous infusion

For IV infusion, CEFTRIAXONE 2 g FKSA is dissolved in 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 6-10 % infusion
- sterile water for injection.

The infusion should be given over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

CEFTRIAXONE FKSA solutions 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. See section 6.2 for incompatibilities.

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

7. Holder of the Certificate of Registration

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Telephone number: +27 (0)11 545 0000

8. Registration number(s)

CEFTRIAXONE 500 mg FKSA: 48/20.1.1/0227

CEFTRIAXONE 1 g FKSA: 48/20.1.1/0228

CEFTRIAXONE 2 g FKSA: 48/20.1.1/0229

9. Date of first authorisation/renewal of the authorisation

02 February 2021

10. Date of revision of the text

15 September 2025