# CLEAN PROPOSED PROFESSIONAL INFORMATION

## SCHEDULING STATUS

**S4**

## 1. NAME OF THE MEDICINE

**CEFUROXIME 750 mg FKSA** Powder for solution for Injection

**CEFUROXIME 1 500 mg FKSA** Powder for solution for Injection or Infusion

## 2. QUALITITATIVE AND QUANTITATIVE COMPOSITION

CEFUROXIME 750 mg FKSA:

Each vial contains 750 mg cefuroxime (as cefuroxime sodium).

Sodium content: 41,4 mg ≈ 1,8 mmol/vial.

CEFUROXIME 1 500 mg FKSA:

Each vial contains 1 500 mg cefuroxime (as cefuroxime sodium).

Sodium content: 82,8 mg ≈ 3,6 mmol/vial.

Sugar free

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection

A white or almost white powder in a vial/infusion bottle

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

CEFUROXIME FKSA is indicated for the treatment of following infections caused by susceptible organisms:

- Respiratory tract infections
- Ear, nose and throat infections
- Urinary tract infections
- Soft tissue infections
- Obstetrics and gynaecological infections
- Gonorrhoea
- Prophylaxis against infection in abdominal, gynaecological, cardiac and pulmonary surgery where there is increased risk for infection.

Sensitivity tests should be carried out whenever possible.

*In vitro* sensitivity does not imply *in vivo* efficacy (clinical).

**CEFUROXIME FKSA has activity against the following organisms:**

- *Staphylococcus aureus* including penicillin-resistant strains, but not rare methicillin-resistant strains
- *Escherichia coli*
- *Klebsiella* spp.
- *Enterobacter* spp.
- *Streptococcus pyogenes*
- *Streptococcus viridans*
- *Clostridium* spp.
- *Proteus mirabilis*
- *Proteus rettgeri*
- *Proteus vulgaris*

- *Proteus morganii*
- *Neisseria* spp. – including β-lactamase producing strains of *N. gonorrhoeae*
- *Haemophilus influenzae*
- *Bacteroides fragilis*
- *Staphylococcus epidermidis*

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

## 4.2 Posology and method of administration

**Posology**

**General dosage recommendation:**

***Adults:***

Dosage range for CEFUROXIME FKSA lies between 1,5 to 6,0 g/day. Many infections will respond to 750 mg three times daily by intramuscular or intravenous injection. For more severe infections, this dose should be increased to 1,5 g three times daily intravenously. The frequency of intramuscular or intravenous injections can be increased to six hourly if necessary.

***Infants > 3 months and children:***

Doses of 30 to 60 mg/kg/day, increased to 100 mg/kg/day if necessary, given in 3 or 4 divided doses. A dose of 60 mg/kg/day will be appropriate for most infections.

**Other recommendations:**

***Gonorrhoea:***

1,5 g CEFUROXIME FKSA should be given as a single dose. This may be given as 2 x 750 mg injections into different sites, e.g. each buttock.

Prophylaxis (surgical infections):

***Abdominal and gynaecological operations:***

The usual dose is 1,5 g CEFUROXIME FKSA intravenously with induction of anaesthesia and may be supplemented by 2 x 750 mg intramuscular doses 8 and 16 hours later.

***Cardiac and pulmonary operations:***

The usual dose is 1,5 g intravenously with induction of anaesthesia, continuing with 750 mg intramuscularly three times daily for a further 24 to 48 hours.

**Special populations**

***Dosage in impaired renal function:***

The dosage of CEFUROXIME FKSA should be reduced in patients with impaired renal function to compensate for its slower excretion. It is not necessary to reduce the dose until the GFR falls below 20 mL/min.

| **Creatinine clearance (mL/min) / (mL/sec)** | **Dose (base)** |
|---|---|
| 10 – 20 | 750 mg every 12 hours |
| < 10 | 750 mg every 24 hours |
| Haemodialysis patients | 750 mg at the end of each dialysis period |
| Continuous peritoneal dialysis patients | 750 mg every 12 hours |

**Method of administration**

**Intramuscular injection**

See Posology.

For instructions on preparation of CEFUROXIME FKSA, see section 6.6.

Suspensions which appear granular must be discarded.

**Intravenous injection**

CEFUROXIME FKSA may be given by slow intravenous injection over 3 to 5 minutes.

When reconstituted the white to almost white powder gives a colourless to slightly yellow solution.

Inspect the reconstituted solution visually for particulate matter and discolouration prior to administration. The reconstituted solution must be clear. For single use only. Any remaining solution should be discarded.

For instructions on preparation of CEFUROXIME FKSA before administration, see section 6.6.

**Intravenous infusion**

For short intravenous infusion (30 to 60 minutes) 1,5 g may be dissolved in 50 mL sterile water for injection. These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids. Solutions which appear turbid must be discarded.

For information on compatible intravenous fluids, see section 6.6.

For instructions on preparation of CEFUROXIME FKSA before administration, see section 6.6.

## 4.3 Contraindications

- Hypersensitivity to cephalosporin antibiotics or to any component of the formulation, listed in section 6.1.
- Hypersensitivity to penicillin and other β-lactam antibiotics.

## 4.4 Special warnings and precautions for use

**Hypersensitivity reactions**

Before CEFUROXIME FKSA is used, careful examination should be made concerning previous hypersensitivity reactions to cephalosporins, penicillins or other medicines.

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

Severe cutaneous adverse reactions (SCARS)

Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of cefuroxime, treatment with cefuroxime must not be restarted in this patient at any time.

**CEFUROXIME FKSA should be used with caution in patients with:**

- A history of gastrointestinal disease, especially ulcerative colitis, regional enteritis or pseudomembranous colitis.
- Hepatic impairment or poor nutritional state.

- Renal function impairment – a reduced dose may be required.
- Porphyria: safety has not been established.

**Overgrowth of non-susceptible microorganisms**

Prolonged use of CEFUROXIME FKSA may result in the overgrowth of non-susceptible organisms (e.g. enterococci and *Clostridioides difficile)*.

Pseudomembranous colitis may occur which may range in severity from mild to life threatening. Patients who develop abdominal or stomach cramps, abdominal tenderness, severe and watery diarrhoea (which may be bloody) and fever, should be investigated for this diagnosis. If the diagnosis of pseudomembranous colitis is suspected, CEFUROXIME FKSA should be stopped immediately and appropriate therapy initiated. Medicines that inhibit peristalsis should not be given.

**Intracameral use and eye disorders**

CEFUROXIME FKSA is not formulated for intracameral use. Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intracameral use of cefuroxime sodium compounded from vials approved for intravenous/intramuscular administration. These reactions included macular oedema, retinal oedema, retinal detachment, retinal toxicity, visual impairment, visual acuity reduced, vision blurred, corneal opacity and corneal oedema.

**Intra-abdominal infections**

Due to its spectrum of activity, CEFUROXIME FKSA is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria (see section 5.1).

**Other medicines**

Do not administer CEFUROXIME FKSA simultaneously with other medicines.

**Concurrent treatment with potent diuretics or aminoglycosides**

Concomitant use of CEFUROXIME FKSA and furosemide should be avoided, if possible. If these medications must be used together, renal function should be monitored closely as furosemide may enhance the nephrotoxic potential of CEFUROXIME FKSA.

The combined use CEFUROXIME FKSA and aminoglycosides seems to increase the risk of nephrotoxicity and must be taken with caution and close monitoring of renal function.

**Interference with serological testing**

The development of a positive Coombs Test associated with the use of cefuroxime may interfere with cross matching of blood (see section 4.8).

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

**Paediatric use**

Safety and effectiveness have not been established in paediatric patients aged 3 months and younger.

**Important information about sodium**

CEFUROXIME 750 mg FKSA contains 41,4 mg sodium per vial, equivalent to 2,1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

CEFUROXIME 1500 mg FKSA contains 82,8 mg sodium per 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

Cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Concomitant use with oral anticoagulants may give rise to increased international normalised ratio (INR).

The following medicine interactions may occur when using CEFUROXIME FKSA:

- Aminoglycoside antibiotics – may result in nephrotoxicity.
- Diuretics – renal function may be affected, thereby affecting elimination.
- Probenecid – concurrent administration of probenecid reduces renal clearance of cefuroxime.
- Concomitant use of cefuroxime and furosemide should be avoided when possible. If they are used together renal function should be monitored closely as furosemide may enhance the nephrotoxic potential of the cephalosporins.

Interactions with laboratory tests:

The following have been selected on the basis of their potential clinical significance, with diagnostic test results:

- Antiglobulin tests (Coomb's tests) – a positive reaction may occur (see section 4.4).
- Benedict's solution, CLINITEST® tablets or Fehling's solution – a false positive reaction for glucose in the urine may occur (see section 4.4).
- Ferricyanide test – a false negative result for blood plasma glucose may occur (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Cefuroxime has been shown to cross the placenta after intramuscular or intravenous dose to the mother.

Safety in pregnancy has not been established.

**Breastfeeding**

Cefuroxime is excreted in human milk in small quantities.

Safety of breastfeeding has not been established.

**Fertility**

There are no data on the effects of cefuroxime on fertility in humans.

## 4.7 Effects on ability to drive or use machines

CEFUROXIME FKSA is not expected to have an influence on the ability to drive or use machines, but patients should not drive, use machinery or perform any tasks that require concentration until they are certain that CEFUROXIME FKSA does not adversely affect their ability to do so safely (see section 4.8).

## 4.8 Undesirable effects

**Summary of the safety profile**

The most frequent adverse reactions are neutropenia, eosinophilia, transient rise in liver enzymes or bilirubin, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver and injection site reactions.

**Tabulated list of adverse reactions**

| **Infections and infestations** | |
|---|---|
| *Frequency unknown:* | *Candida* overgrowth, overgrowth of *Clostridioides difficile* |

| | |
|---|---|
| **Blood and lymphatic system disorders:** | |
| *Frequent:* | Neutropenia, eosinophilia, decreased haemoglobin concentration |
| *Less frequent:* | Leucopenia, thrombocytopenia, hypoprothrombinaemia, haemolytic anaemia |
| *Frequency unknown:* | Agranulocytosis, pancytopenia |
| **Immune system disorders:** | |
| *Less frequent*: | Hypersensitivity reactions including skin rashes, urticaria, pruritus, bronchospasm, drug fever, serum sickness, anaphylaxis, angioedema, cutaneous vasculitis |
| **Nervous system disorders:** | |
| *Frequent:* | Headache |
| *Less frequent:* | Seizures |
| **Ear and labyrinth disorders:** | |
| *Less frequent:* | Mild to moderate hearing loss |
| **Cardiac disorders:** | |
| *Frequency unknown:* | Kounis syndrome |
| **Gastrointestinal disorders:** | |
| *Less frequent*: | Nausea; vomiting; abdominal pain; diarrhoea, in some cases accompanied by blood in the stools, which may be a symptom of enterocolitis. A particular form of enterocolitis is pseudomembranous colitis (see section 4.4). |
| **Hepato-biliary disorders:** | |
| *Frequent:* | Transient rise in liver enzymes |
| *Less frequent:* | Transient rise in bilirubin |

| | |
|---|---|
| *Frequencies unknown:* | Hepatic dysfunction including cholestasis |
| **Skin and subcutaneous disorders:** | |
| *Less frequent:* | Skin rash, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, pruritus |
| *Frequency unknown:* | Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) |
| **Renal and urinary disorders:** | |
| *Less frequent*: | Interstitial nephritis |
| *Frequency unknown:* | Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4) |
| **General disorder and administrative site conditions:** | |
| *Frequent*: | Injection site reactions which may include pain and thrombophlebitis |
| **Investigations**: | |
| *Less frequent:* | The use of CEFUROXIME FKSA may be accompanied by a false positive Coomb's test. This may interfere with the performance of cross tests with blood (see section 4.5). |

**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

Symptoms of overdose:

Overdose can cause cerebral irritation leading to convulsions.

Treatment of overdose:

Treatment is symptomatic and supportive. Serum levels of CEFUROXIME FKSA can be reduced by haemodialysis or peritoneal dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A 20.1.1 – Broad and medium spectrum antibiotics

Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins, ATC code J01DC02.

Cefuroxime is a bactericidal semi-synthetic, second-generation cephalosporin. Cefuroxime has bactericidal activity against a wide range of Gram positive and Gram negative aerobic and anaerobic organisms. The mechanism of action of cefuroxime results from inhibition of cell-wall synthesis and is highly stable in the presence of β-lactamases.

**The following bacteria show resistance to cefuroxime:**

Most strains of enterococci, e.g., *Enterococcus faecalis*

Methicillin-resistant staphylococci and *Listeria monocytogenes*

Some strains of *Morganella morganii*, *Enterobacter cloacae*, and *Citrobacter* spp.

*Pseudomonas* and *Campylobacter* spp., *Legionella* spp., *Acinetobacter calcoaceticus*, and most strains of *Serratia* spp. and *Proteus vulgaris*.

*Clostridium difficile* and most strains of *Bacteroides fragilis*.

### 5.2 Pharmacokinetic properties:

Peak serum levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes.

Concurrent administration of probenecid produces an elevated peak serum level and restricts the excretion of the antibiotic.

There is almost complete recovery of unchanged cefuroxime in the urine within 24 hours of administration, the major part being eliminated in the first six hours. The tubular excretion component of renal clearance of cefuroxime is of the order of 50 %.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None.

### 6.2 Incompatibilities

The pH of 2,74 % *m/v* Sodium bicarbonate injection considerably affects the colour of the solution and is therefore not recommended for the dilution of CEFUROXIME FKSA.

However, if required for patients receiving Sodium bicarbonate injection by infusion, CEFUROXIME FKSA may be introduced into the tube of the giving set.

In the absence of other compatibility studies, CEFUROXIME FKSA must not be mixed with other medicines apart from those listed as compatible in section 6.6.

## 6.3 Shelf life

Sterile powder for injection: 24 months

After reconstitution:

From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 5 hours at 25 °C and for 24 hours at 2-8 °C.

## 6.4 Special precautions for storage

Sterile powder: Store at or below 25 °C. Keep the vials in outer carton to protect from light at or below 25 °C.

Reconstituted product: For storage conditions after reconstitution of the product, see section 6.3.

Some change in colour may occur on storage.

## 6.5 Nature and contents of container

CEFUROXIME 750 mg FKSA:

15 mL type II, clear, colourless glass vial closed with grey rubber stoppers and blue aluminium/ plastic caps, in packs of 10.

CEFUROXIME 1 500 mg FKSA:

20 mL type II, clear, colourless glass vials closed with red rubber stoppers and red aluminium/plastic caps, in packs of 10.

50 mL type II, clear, colourless glass infusion bottles closed with dark grey rubber stoppers and red aluminium/plastic caps, in packs of 10.

## 6.6 Special precautions for disposal and other handling

**Intravenous injection:**

Dissolve CEFUROXIME FKSA in sterile water for injection, at least 6 mL for 750 mg, and at least 15 mL for 1 500 mg. Solutions which appear turbid must be discarded.

When reconstituted the white to almost white powder gives a colourless to slightly yellow solution.

Some change in colour may occur on storage. The reconstituted solution must be clear. For single use only. Any remaining solution should be discarded.

**Intravenous infusion:**

For short intravenous infusion (30 to 60 minutes) 1,5 g may be dissolved in 50 mL sterile water for injection. These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids. Solutions which appear turbid must be discarded.

CEFUROXIME FKSA is compatible with the more commonly used intravenous fluids. It will retain potency for up to 5 hours at 25 °C or 24 hours at 2 - 8 °C in Water for injection, Sodium chloride injection 0,9 % *m/v* and 5 % Dextrose injection. The stability of CEFUROXIME FKSA in Sodium chloride injection 0,9 % *m/v* and in 5 % Dextrose injection is not affected by the presence of hydrocortisone sodium phosphate.

CEFUROXIME FKSA is also compatible with aqueous solutions containing up to 1 % lidocaine (lignocaine) hydrochloride.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

162 Tonetti Street

Stand 7, Growthpoint Business Park

Halfway House, Midrand, 1685

South Africa

## 8. REGISTRATION NUMBERS

CEFUROXIME 750 mg FKSA: 42/20.1.1/0737

CEFUROXIME 1 500 mg FKSA: 42/20.1.1/0986

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of registration: 07 December 2012

## 10. DATE OF REVISION OF THE TEXT

To be confirmed