

SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the medicinal product

SEFOXIM 1000- Cefotaxime for Injection USP

2. Qualitative and quantitative composition

Each vial contains:

Cefotaxime sodium USP

Eq. to Cefotaxime..... 1000 mg

For excipients see 6.1.

3. Pharmaceutical form

Dry powder for Injection

Off-white to pale yellow crystalline powder

4. Clinical particulars

4.1 Therapeutic indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Cefotaxime sodium is indicated for the treatment of the following severe infections when known or thought very likely to be due to organisms that are susceptible to cefotaxime.

- Infections of the lower respiratory tract
- Infections of the kidneys and urinary tract
- Infections of the skin and soft tissue
- Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable
- Intra-abdominal infections (including Peritonitis)
- Lyme-borreliosis (especially stages II and III)
- Acute Meningitis in case of gram-negative microorganisms in combination with another suitable antibiotic
- Sepsis in case of gram-negative microorganism in combination with another suitable antibiotic
- Endocarditis in case of gram-negative microorganism in combination with another suitable antibiotic

Peri-operative prophylaxis in surgical procedures such as colorectal, gastrointestinal, prostatic, urogenital and gynaecological surgery in patients who have a definite risk of post-operative infections. Cefotaxime should be used in combination with another antibiotic that can provide anaerobic cover in the treatment of intra-abdominal infections. Cefotaxime should be used in combination with an aminoglycoside in the treatment of infections caused by *Pseudomonas*.

Protection is best insured by achieving adequate local tissue concentrations at the time contamination is likely to occur.

Administration should usually be stopped within 24 hours since continuing use of any antibiotic in the majority of surgical procedures does not reduce the incidence of subsequent infection.

4.2 Posology and method of administration

Cefotaxime sodium may be administered intravenously, by bolus injection or infusion, or intramuscularly. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

The clinician should consult published protocols for information on dosage regimens in specific conditions such as gonorrhoea, *Pseudomonas* infections and CNS infections.

Dosage and type of administration depend on the severity of the infection, the sensitivity of the bacterium and the condition of the patient.

The duration of the treatment depends on the course of the disease. As a general rule Cefotaxime is administered for a further 3 to 4 days after improvement/regression of the symptoms.

Adults and children over 12 years in general receive 1 g Cefotaxime every 12 hours. In severe cases, the daily dose can be increased up to 12 g. Daily doses up to 6 g can be divided into at least two individual administrations at 12 hourly intervals. Higher daily doses must be divided into at least 3 to 4 individual administrations at 8 or 6 hour intervals respectively.

The following table may serve as a guide to dosages:

Type of Infection	Single Dose Cefotaxime	Dose Interval	Daily Dose Cefotaxime
Typical infections, in which sensitivity is demonstrated and bacterium is proven or suspected	1 g	12 h	2 g
Infections, in which various bacteria with high to medium sensitivity are demonstrated or suspected	2 g	12 h	4 g
Unclear bacterial illness which cannot be	2 – 3 g	8 h	6 g

localised and where the patient is critically ill		up to 6 h up to 6 h	up to 8 g up to 12 g
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For the treatment of gonorrhoea in adults, 1 vial of Cefotaxime Sodium for Injection 500mg administered as a single administration.

In most cases due to less sensitive infective bacteria, an increase may be necessary, i.e. 1 g Cefotaxime. Examination for syphilis needs to be carried out before commencing therapy.

Perioperative Prophylaxis

For peri-operative infection prophylaxis the administration of a single dose of 1 to 2 g Cefotaxime 30 to 60 minutes prior to the operation is recommended. Another antibiotic to cover anaerobic organisms is necessary. A repeat dose is required if the duration of the operation exceeds 90 minutes.

Special Dose Recommendations

Lyme borrelisosis: A daily dose of 6 g Cefotaxime (14 to 21 days duration). The daily dose was generally administered divided into 3 parts (2 g Cefotaxime 3 times daily).

Infants and children up to 12 years receive 50 to 100 mg Cefotaxime according to the severity of the infection (up to 150 mg) per kilogram of body weight per day, divided into equal doses, administered at 12 (up to 6) hour intervals. In individual cases – particularly in life threatening situations – it may be necessary to increase the daily dose to 200 mg Cefotaxime per kilogram of body weight.

In neonates and infants doses of 50 mg Cefotaxime per kilogram of body weight per day should not be exceeded in view of not fully matured kidney clearance.

In case of life-threatening situations it may be necessary to increase the daily dose.

In those situations the following table is recommended.

Age	Daily Dose of Cefotaxime
0 - 7 days	50 mg/kg every 12 hours IV
7 days - 1 month	50 mg/kg every 8 hours IV
> 1 month	75 mg/kg every 8 hours IV

It is not necessary to differentiate between premature and normal-gestational age infants.

Dosage in the Case of Impaired Renal Function

With patients with a creatinine clearance of 20ml/minute or less, the maintenance dose is reduced to half the normal dose. With patients with a creatinine clearance of 5 ml/minute or less, a reduction of the maintenance dose to 1 g Cefotaxime (divided into 2 individual administrations at 12 hour intervals), seems to be appropriate. The stated recommendations are based on experiences with adults.

Since Cefotaxime is to a large extent eliminated by haemodialysis, an additional dose should be administered to patients who are dialysed, after the dialysis procedure.

Elderly Patients

No dosage adjustments are needed in patients with normal function.

Other Advice

Electrolyte content of the injections solutions: Since Cefotaxime is available as the sodium salt, the sodium content per dose should be taken into account within the framework of the overall therapy and with special balance checks.

Basis for calculation: 1 g Cefotaxime (equivalent to 1.04 g Cefotaxime sodium) should be calculated as 48 mg sodium equivalent to 2.1 mmol sodium.

Posology and Method of Administration

Intravenous Injection

For IV, Cefotaxime Sodium for Injection 500mg is dissolved in at least 2 ml water for injections, Cefotaxime Sodium for Injection 1 g in at least 4 ml and subsequently injected directly into the vein over 3 to 5 minutes or after clamping of the infusion tube into the distal end of the tube.

During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter.

Infusion

For brief infusion 2g of Cefotaxime Sodium for Injection is dissolved in 100 ml of isotonic sodium chloride or glucose solution and subsequently IV infused over 50 to 60 minutes. Another compatible infusion solution can also be used for the solution.

Intramuscular Injection

For intramuscular injection. Cefotaxime Sodium for Injection 500mg is dissolved in 2 ml and Cefotaxime Sodium for Injection 1 g in 4 ml water for injections respectively. Afterwards the injection should take place deep into the gluteal muscle. Pain with the IM injection can be avoided by dissolving Cefotaxime Sodium for Injection 500mg in 2ml or Cefotaxime Sodium for Injection 1 g in 4 ml 1% lidocaine solution. An intravascular injection is to be avoided in this case, since with intravascular administration lidocaine may lead to unrest, tachycardia, disturbances of cardiac conduction as well as vomiting and cramp. Cefotaxime reconstituted with lidocaine should not be administered to infants under 30 months.

It is recommended that no more than 4 ml be injected unilaterally. If the daily dose exceeds 2 g Cefotaxime or if Cefotaxime is injected more frequently than twice per day, the IV route is recommended.

Combination Therapy

Combination therapy of Cefotaxime with aminoglycosides is indicated without availability of an antibiogram in the case of severe, life-threatening infections. Kidney function must be

watched in such combination usage. Cefotaxime and aminoglycosides should not be mixed in the same syringe or infusion fluid.

In cases of infections with *Pseudomonas aeruginosa* combination with other antibiotics effective against *Pseudomonas* can also be indicated.

For infection prophylaxis (peri-operative prophylaxis in surgical procedures such as colorectal, gastro-intestinal, prostatic, urogenital, obstetric and gynaecological surgery) in patients with weakened defence mechanisms, combination can also be indicated with other suitable antibiotics.

4.3 Contraindications

Known or suspected hypersensitivity to Cefotaxime or other cephalosporins. Allergic cross-reactions can exist between penicillins and cephalosporins (see section 4.4).

Cefotaxime constituted with Lidocaine Injection BP must never be used:

- by the intravenous route
- in infants under 30 months of age
- in subjects with a previous history of hypersensitivity to Lidocaine or other local anaesthetics of the amide type
- in patients who have a non-paced heart block
- in patients with severe heart failure.

4.4 Special warnings and precautions for use

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patients condition is essential. If superinfection occurs during treatment, appropriate measures should be taken.

Anaphylactic reactions

Cefotaxime should be used with caution in persons with a history of allergies or asthma.

Preliminary enquiry about hypersensitivity to penicillin and other β -lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases. Use of cephalosporins should be undertaken with extreme caution in penicillin-sensitive subjects

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal (see sections 4.3 and 4.8). If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contraindicated in subjects with a history of immediate-type hypersensitivity to cephalosporins.

Serious bullous reactions

Cases of serious bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

***Clostridium difficile* associated disease (e.g. pseudomembranous colitis)**

Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of *Clostridium difficile* associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis.

The diagnosis of this rare but potentially fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay.

Clostridium difficile associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

Haematological reactions

Leucopenia, neutropenia and more rarely, agranulocytosis, may develop during treatment with cefotaxime, particularly if given over long periods. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.

Some case of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anaemia have also been reported (see section 4.8).

Patients with renal insufficiency

The dosage should be modified according to the creatinine clearance calculated.

Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly and those with pre-existing renal impairment.

Neurotoxicity

High doses of beta lactam antibiotics including cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

Precautions for administration

During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2).

See section 4.3 for contraindications for formulations reconstituted with lidocaine.

Effects on Laboratory Tests

As with other cephalosporins, a positive Coombs test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood.

Urinary glucose testing with non-specific reducing agents may yield false positive results. This phenomenon is not seen when a glucose-oxidase specific method is used.

Sodium intake

The sodium content of this product (48.2 mg/g) should be taken into account when prescribing to patients requiring sodium restriction.

4.5 Interaction with other medicinal products and other forms of interaction

Cefotaxime / Other Antibiotics

As far as possible, Cefotaxime should not be combined with substances having a bacteriostatic action (e.g. tetracycline, erythromycin, chloramphenicol or sulfonamides), since antagonistic effect has been observed regarding the anti-bacterial effect in vitro. A synergistic effect can result with the combination with aminoglycosides.

An increased risk of oto- and nephrotoxicity has been reported when cefotaxime has been used concomitantly with cephalosporins or aminoglycosides. Dose adjustment may be necessary, and the kidney function must be watched (see 4.2 Posology).

Cefotaxime / Probenecid

The simultaneous administration of Probenecid leads to higher, more prolonged plasma concentrations of Cefotaxime by interfering with renal tubular transfer thereby delaying excretion.

Cefotaxime / Potentially Nephrotoxic Drugs and Loop Diuretics.

In combination with potentially nephrotoxic drugs (such as, for example, aminoglycoside antibiotics, polymyxin B and colistin) and with potent diuretics, (e.g. furosemide) the kidney function should be monitored (see section 4.4), since the nephrotoxicity of the substances quoted may be accentuated.

Influence on Laboratory Diagnostic Tests

False positives may occur in the Coombs-Test in rare cases during treatment with cefotaxime.

In glucose determinations in urine and blood, false positive as well as false negative results may also be obtained, depending on the method; these may be avoided by the use of enzymatic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of cefotaxime has not been established in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are however no adequate and well controlled studies in pregnant women.

Cefotaxime passes through the human placenta. Therefore, Cefotaxime should only be used during pregnancy if the anticipated benefit outweighs any potential risks.

Lactation

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, colonisation by yeast-like fungi and may also lead to sensitisation of the infant. Therefore a decision must be made whether to discontinue breast-feeding or to discontinue therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

4.7 Effects on ability to drive and use machines

There is no evidence that cefotaxime impairs the ability to drive or operate machinery.

High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

Adverse reactions to cefotaxime sodium have occurred relatively infrequently and have generally been mild and transient.

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)*
Infections and infestation						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leucopenia, Eosinophilia, Thrombocytopenia			Neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions, angioedema, bronchospasm,

						anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache, dizziness, encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastro-intestinal disorders			Diarrhoea			Nausea, vomiting, abdominal pain, pseudomembranous colitis (see section 4.4)
Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash, pruritis, urticaria			Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4)
Renal and urinary disorders			Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)			Interstitial nephritis
General disorders and administration	Pain at the injection		Fever Inflammatory reactions at the			Systemic reactions to lidocaine (if reconstituted with

site conditions	site		injection site including phlebitis, thrombophlebitis			lidocaine)
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* post-marketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment. The occurrence of one or more of the following symptoms has been reported after several weeks of treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty in breathing, joint discomfort

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

4.9 Overdose

Symptoms of Overdose

Intoxication in the strictest sense, is not known in man. Symptoms of overdose may largely correspond to the profile of side effects. With certain risk patterns and with the administration of very high doses, there is a risk of reversible encephalopathy, central nervous system excitation conditions, myoclonia and cramp, as have been described for other beta lactams. The risk of the appearance of these undesirable effects is increased in patients with severely restricted kidney function, epilepsy and meningitis.

Emergency Measures

In case of overdose, cefotaxime must be discontinued and supportive treatment initiated, which includes measures to accelerate elimination and symptomatic treatment of adverse reactions e.g. convulsions.

Drug initiated cramps can be treated with diazepam or phenobarbital, but not with phenytoin. With anaphylactic reactions the usual emergency measures must be commenced, preferably with the first indications.

No specific antidote exists. Plasma levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Classification

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins.

ATC Code: J01D D01

Mode of action

Cefotaxime exerts its action by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thereby inhibiting cell wall synthesis.

Mechanisms of resistance

Resistance to Cefotaxime may be due to one or several of the following mechanisms:

- production of extended-spectrum beta-lactamases (ESBLs)
- induction and/or constitutive expression of AmpC beta- lactamases
- reduced outer membrane permeability
- efflux pump mechanisms.
- Modification of target enzymes (altered PBPs)

More than one of these mechanisms may co-exist in a single bacterium.

PK/PD relationship

Efficacy mainly depends on time above the minimal inhibitory concentration of cefotaxime for the pathogen(s) to be treated (T/MIC).

Breakpoints:

Current MIC breakpoints used to interpret cefotaxime susceptibility data are shown below.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (V1.1, 31/03/2006)

	Susceptible (<)/ Resistant (>)
<i>Enterobacteriaceae</i> ²	1/2
<i>Pseudomonas</i>	--
<i>Acinetobacter</i>	--
<i>Staphylococcus</i> ³	Note ³
<i>Enterococcus</i>	--
<i>Streptococcus A, B, C, G</i>	0.5/0.5 ⁴
<i>Streptococcus pneumoniae</i>	0.5/2 ⁴
<i>Haemophilus influenzae</i> <i>Moraxella Catarrhalis</i>	0.12/0.12 ⁴
<i>Neisseria gonorrhoea</i>	0.12/0.12 ⁴
<i>Neisseria Meningitidis</i>	0.12/0.12 ⁴
<i>Gram-negative, anaerobes</i>	--
Non-species related breakpoints ¹	1/2

S ≤ / > R	
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1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).

4. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = rationale document listing data used by EUCAST for determining breakpoints.

Commonly susceptible species

Gram-positive aerobes
<i>Staphylococcus aureus</i> (Methicillin-susceptible)^*
Group A Streptococci (including <i>Streptococcus pyogenes</i>) *
Group B Streptococci
β-hemolytic Streptococci (Group C, F, G)
Viridans Group Streptococci
Gram-negative aerobes
<i>Haemophilus influenzae</i> *
<i>Haemophilus parainfluenzae</i> *
<i>Moraxella catarrhalis</i> *
<i>Neisseria gonorrhoeae</i> *
<i>Neisseria meningitidis</i> *
<i>Proteus</i> spp. *
<i>Providencia</i> spp. *
<i>Yersinia enterocolitica</i>

Anaerobes
<i>Clostridium</i> spp. (not <i>Clostridium difficile</i>)
<i>Peptostreptococcus</i> spp.
<i>Propionibacterium</i> spp.
Others
Species for which acquired resistance may be a problem
<i>Streptococcus pneumoniae</i>
<i>Citrobacter</i> spp*
<i>Enterobacter</i> spp*
<i>Klebsiella</i> spp*
<i>Escherichia coli</i> *
<i>Serratia</i> spp
<i>Morganella morganii</i>
<i>Streptococcus pneumoniae</i> *
<u>Inherently resistant organisms</u>
Gram-positive aerobes
<i>Enterococcus</i> spp.
<i>Enterococcus faecalis</i>
<i>Enterococcus faecium</i>
<i>Listeria</i> spp.
Gram-negative aerobes
<i>Acinetobacter</i> spp.
<i>Pseudomonas</i> spp.
<i>Stenotrophomonas maltophilia</i>
Anaerobes
<i>Bacteroides</i> spp.
<i>Clostridium difficile</i>
<u>Others</u>
<i>Chlamydiae</i>
<i>Mycoplasma</i> spp.
<i>Legionella pneumophila</i>

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

^Methicillin-(oxacillin) resistant staphylococci (MRSA) are always resistant to cefotaxime.

Penicillin-resistant *Streptococcus pneumoniae* show a variable degree of resistance to cephalosporins such as cefotaxime.

5.2 Pharmacokinetic properties

After a 1000 mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500 mg and 2000 mg produce plasma concentrations of 38 and 200 microgram /ml, respectively. There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of cefotaxime is 21.6 litres/1.73 m² after 1 g intravenous 30 minute infusion.

Concentrations of cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 microgram/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier at levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 microgram/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390 ml/minute and renal clearance 145 to 217 ml/minute.

After intravenous administration of cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to the data already provided in other sections of this Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Glass Vial

6.6 Special precautions for disposal and other handling

Following reconstitution: Cefotaxime sodium is compatible with the following diluents:

Water for Injections, Sodium Chloride 0.9% , Dextrose 5 and 10% , Ringer's Solution

Ringer-Lactate Solution , Lignocaine 1% (only freshly prepared solutions should be used)

7. Marketing authorisation holder

SAKAR Healthcare Limited

Block No. 10-13, Sarkhej-Bavla Highway,

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8. Marketing authorisation number(s)

05557/4467/NMR/2017

9. Date of first authorisation/renewal of the authorisation

16/12/2020

10. Date of revision of the text

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Stock Availability

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Summary of Product Characteristic

1. Name of the medicinal product

CEFROTIL 750 - Cefuroxime for Injection USP

2. Qualitative and quantitative composition

Each vial contains:

Cefuroxime Sodium USP

Equivalent to Cefuroxime 750 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dry powder for Injection

White or faintly yellow powder

4. Clinical particulars

4.1 Therapeutic indications

Cefuroxime powder for solution for injection or infusion is indicated for the treatment of infections listed below in adults and children, including neonates (from birth) (see sections 4.4 and 5.1).

- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis
- Complicated urinary tract infections, including pyelonephritis
- Soft-tissue infections: cellulitis, erysipelas and wound infections
- Intra-abdominal infections (see section 4.4)

- Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section)

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Table 1. Adults and children ≥ 40 kg

Indication	Dosage
Community acquired pneumonia and acute exacerbations of chronic bronchitis	750 mg every 8 hours (intravenously or intramuscularly)
Soft-tissue infections: cellulitis, erysipelas and wound infections.	
Intra-abdominal infections	
Complicated urinary tract infections, including pyelonephritis	1.5 g every 8 hours (intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
Surgical prophylaxis for gastrointestinal, gynaecological surgery (including caesarean section) and orthopaedic operations	1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.
Surgical prophylaxis for cardiovascular and oesophageal operations	1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.

Table 2. Children < 40 kg

	Infants and toddlers > 3 weeks and children < 40 kg	Infants (birth to 3 weeks)
Community acquired pneumonia	30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60 mg/kg/day is appropriate for most infections	30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses (see section 5.2)
Complicated urinary tract infections, including pyelonephritis		
Soft-tissue infections: cellulitis, erysipelas and wound infections		

Intra-abdominal infections		
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Renal impairment

Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of Cefuroxime should be reduced to compensate for its slower excretion.

Table 3. Recommended doses for Cefuroxime in renal impairment

Creatinine clearance	T_{1/2} (hrs)	Dose mg
> 20 mL/min/1.73 m ²	1.7-2.6	It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily).
10-20 mL/min/1.73 m ²	4.3-6.5	750 mg twice daily
< 10 mL/min/1.73 m ²	14.8-22.3	750 mg once daily
Patients on haemodialysis	3.75	A further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis; in addition to parenteral use, cefuroxime sodium can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).
Patients in renal failure on continuous arteriovenous haemodialysis (CAVH) or high-flux haemofiltration (HF) in intensive therapy units	7.9-12.6 (CAVH) 1.6 (HF)	750 mg twice daily; for low-flux haemofiltration follow the dosage recommended under impaired renal function.

Hepatic impairment

Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is not expected to effect the pharmacokinetics of cefuroxime.

Method of administration

Cefuroxime should be administered by intravenous injection over a period of 3 to 5 minutes directly into a vein or via a drip tube or infusion over 30 to 60 minutes, or by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 750 mg should be injected at one site. For doses greater than 1.5 g intravenous administration should be used. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

750 mg powder for solution for infusion.

For instructions on preparation of the medicinal product before administration, see section 6.6

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.

Patients with known hypersensitivity to cephalosporin antibiotics.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. 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). In case of severe hypersensitivity reactions, treatment with cefuroxime 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 cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Cephalosporin antibiotics may, in general, be given safely to patients who are hypersensitive to penicillins, although cross-reactions have been reported. Special care is indicated in patients who have experienced an anaphylactic reaction to penicillin.

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.

Concurrent treatment with potent diuretics or aminoglycosides

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides. Renal impairment has been reported during use of these combinations. Renal function should be monitored in the elderly and those with known pre-existing renal impairment (see section 4.2).

Overgrowth of non-susceptible microorganisms

Use of cefuroxime may result in the overgrowth of *Candida*. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).

Antibacterial agent-associated pseudomembranous colitis has been reported with use of cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime (see section 4.8). Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Intra-abdominal infections

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

Interference with diagnostic tests

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.

Intracameral use and eye disorders

Cefuroxime 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.

Important information about excipients

Cefuroxime powder for solution for injection or infusion contains 40.6 mg sodium per 750mg vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be considered for patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid prolongs the excretion of cefuroxime and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics

High-dosage treatments with cephalosporins should be carried out with caution on patients who are taking strong-acting diuretics (such as furosemide) or potential nephrotoxic preparations (such as aminoglycoside antibiotics), since impairment of renal function through such combinations cannot be ruled out.

Other Interactions

Determination of blood/plasma glucose levels: Please refer to section 4.4.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

System organ class	Common	Uncommon	Not known
<u>Infections and infestations</u>			<i>Candida</i> overgrowth, overgrowth of <i>Clostridium difficile</i>
<u>Blood and lymphatic system disorders</u>	neutropenia, eosinophilia, decreased haemoglobin concentration	leukopenia, positive Coombs test	thrombocytopenia, haemolytic anaemia
<u>Immune system disorders</u>			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
<u>Cardiac disorders</u>			Kounis syndrome
<u>Gastrointestinal disorders</u>		gastrointestinal disturbance	pseudomembranous colitis (see section 4.4)
<u>Hepatobiliary disorders</u>	transient rise in liver enzymes	transient rise in bilirubin	
<u>Skin and subcutaneous tissue disorders</u>		skin rash, urticaria and pruritus	erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome, angioneurotic oedema, Drug Reaction with Eosinophilia and Systemic Symptoms

			(DRESS)
<u>Renal and urinary disorders</u>			elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4)
<u>General disorders and administration site conditions</u>	injection site reactions which may include pain and thrombophlebitis		

Description of selected adverse reactions

Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coombs test (which can interfere with cross matching of blood) and very rarely haemolytic anaemia.

Transient rises in serum liver enzymes or bilirubin have been observed which are usually reversible.

Pain at the intramuscular injection site is more likely at higher doses. However it is unlikely to be a cause for discontinuation of treatment.

There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity (see section 5.3). Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk.

Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of cefuroxime sodium on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of cefuroxime on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

4.8 Undesirable effects

The most common 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.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1,000$ to $< 1/100$; rare $\geq 1/10,000$ to $< 1/1,000$; very rare $< 1/10,000$ and not known (cannot be estimated from the available data).

Paediatric population

The safety profile for cefuroxime sodium in children is consistent with the profile in adults.

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see sections 4.2 and 4.4).

Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases including (but not limited to) extended-spectrum beta-lactamases (ESBLs), and Amp-C enzymes, that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species;
- reduced affinity of penicillin-binding proteins for cefuroxime;
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria;
- bacterial efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime. Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

Cefuroxime sodium breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microorganism	Breakpoints (mg/L)	
	<u>Susceptible</u>	<u>Resistant</u>
<i>Enterobacteriaceae</i> (<i>Enterobacterales</i>) ^{1, 2}	≤8	>8
<i>Staphylococcus</i> spp.	Note ³	Note ³
<i>Streptococcus</i> A, B, C and G	Note ⁴	Note ⁴
<i>Streptococcus pneumoniae</i>	≤0.5	>1
<i>Streptococcus</i> (other)	≤0.5	>0.5
<i>Haemophilus influenzae</i>	≤1	>2
<i>Moraxella catarrhalis</i>	≤4	>8
<i>Kingella kingae</i>	≤0.5	>0.5
Non-species related breakpoints ¹	≤4 ⁵	>8 ⁵

¹ The cephalosporin breakpoints for *Enterobacteriaceae* will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. ESBL detection and characterisation are recommended for public health and infection control purposes.

² Breakpoint relates to a dosage of 1.5 g × 3 and to *E. coli*, *P. mirabilis* and *Klebsiella* spp. only

³ Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections.

⁴ The susceptibility of streptococcus groups A, B, C and G is inferred from the benzylpenicillin susceptibility.

⁵ Breakpoints apply to daily intravenous dose of 750 mg × 3 and a high dose of at least 1.5 g × 3.

Microbiological susceptibility

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 known and the utility of the agent in at least some types of infections is questionable.

Cefuroxime is usually active against the following microorganisms *in vitro*.

Commonly susceptible species
<u>Gram-positive aerobes:</u> <i>Staphylococcus aureus</i> (methicillin-susceptible) \$ <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i>
<u>Gram-negative aerobes:</u> <i>Haemophilus parainfluenzae</i> <i>Moraxella catarrhalis</i>
Microorganisms for which acquired resistance may be a problem
<u>Gram-positive aerobes:</u> <i>Streptococcus pneumoniae</i> <i>Streptococcus mitis</i> (viridans group)
<u>Gram-negative aerobes:</u> <i>Citrobacter</i> spp. not including <i>C. freundii</i> <i>Enterobacter</i> spp. not including <i>E. aerogenes</i> and <i>E. cloacae</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Proteus</i> spp. not including <i>P. penneri</i> and <i>P. vulgaris</i> <i>Providencia</i> spp. <i>Salmonella</i> spp.
<u>Gram-positive anaerobes:</u> <i>Peptostreptococcus</i> spp. <i>Propionibacterium</i> spp.
<u>Gram-negative anaerobes:</u> <i>Fusobacterium</i> spp. <i>Bacteroides</i> spp.
Inherently resistant microorganisms
<u>Gram-positive aerobes:</u> <i>Enterococcus faecalis</i> <i>Enterococcus faecium</i>
<u>Gram-negative aerobes:</u> <i>Acinetobacter</i> spp. <i>Burkholderia cepacia</i> <i>Campylobacter</i> spp. <i>Citrobacter freundii</i> <i>Enterobacter aerogenes</i> <i>Enterobacter cloacae</i> <i>Morganella morganii</i> <i>Proteus penneri</i> <i>Proteus vulgaris</i>

<i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i> <i>Stenotrophomonas maltophilia</i>
<u>Gram-positive anaerobes:</u> <i>Clostridium difficile</i>
<u>Gram-negative anaerobes:</u> <i>Bacteroides fragilis</i>
<u>Others:</u> <i>Chlamydia</i> spp. <i>Mycoplasma</i> spp. <i>Legionella</i> spp.

§ All methicillin-resistant *S. aureus* are resistant to cefuroxime.

In vitro the activities of cefuroxime sodium and aminoglycoside antibiotics in combination have been shown to be at least additive with occasional evidence of synergy.

5.2 Pharmacokinetic properties

Absorption

After intramuscular (IM) injection of cefuroxime to normal volunteers, the mean peak serum concentrations ranged from 27 to 35 µg/mL for a 750 mg dose and from 33 to 40 µg/mL for a 1000 mg dose, and were achieved within 30 to 60 minutes after administration. Following intravenous (IV) doses of 750 and 1500 mg, serum concentrations were approximately 50 and 100 µg/mL, respectively, at 15 minutes.

AUC and C_{max} appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV administration. There was no evidence of accumulation of cefuroxime in the serum from normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been stated as 33 to 50%, depending on the methodology used. The average volume of distribution ranges from 9.3 to 15.8 L/1.73 m² following IM or IV administration over the dosage range of 250 to 1000 mg. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised.

Elimination

Cefuroxime is excreted by glomerular filtration and tubular secretion. The serum half-life after either intramuscular or intravenous administration is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24

hours of administration. The majority of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m² following IM or IV administration over the dosage range of 250 to 1000 mg.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly

Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function (see section 4.2).

Paediatrics

The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment

Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. Cr_{cl} <20 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). Cefuroxime is effectively removed by haemodialysis and peritoneal dialysis.

Hepatic impairment

Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an effect on the pharmacokinetics of cefuroxime.

PK/PD relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. Pharmaceutical particulars

6.1 List of excipients

None.

6.2 Incompatibilities

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions.

The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of Cefuroxime. However, if required, for patients receiving sodium bicarbonate injection by infusion the Cefuroxime solution may be introduced into the tube of the giving set.

Cefuroxime should not be mixed in the syringe with aminoglycoside antibiotics.

In the absence of other compatibility studies, this medicinal product must not be mixed with other medicinal products apart from those listed as compatible in section 6.6.

6.3 Shelf life

2 Years.

6.4 Special precautions for storage

Store Below 30 °C.

6.5 Nature and contents of container

Glass Vial

6.6 Special precautions for disposal and other handling

Instructions for constitution

Table 4. Additional volumes and solution/suspension concentrations which may be useful when fractional doses are required.

Additional volumes and solution/suspension concentrations, which may be useful when fractional doses are required				
Vial size	Routes of administration	Amount of water to be added (mL)	Approximate cefuroxime concentration (mg/mL)**	Resulting product
750 mg	intramuscular	3 mL	216	Suspension
	intravenous bolus	at least 6 mL	116	Solution
	intravenous infusion	at least 6 mL*	116	Solution

** Reconstituted solution to be added to 50 or 100 ml of compatible infusion fluid (see information on compatibility, below)*

*** The resulting volume of the solution/suspension of cefuroxime in reconstitution medium is increased due to the displacement factor of the drug substance resulting in the listed concentrations in mg/ml.*

As for all parenteral medicinal products, inspect the reconstituted solution or suspension visually for particulate matter and discoloration prior to administration.

Intramuscular injection: After addition of the specified amount of diluent for intramuscular injection, a suspension is formed.

Intravenous bolus injection or intravenous infusion: After addition of the specified amount of diluent for intravenous bolus or infusion, a clear solution is formed. The solution should only be used if the solution is clear and practically free from particles.

Solutions and suspensions range in colour from clear to yellow coloured depending on concentration, diluent and storage conditions used. When made up for intramuscular use, it becomes off-white and opaque. When made up for intravenous administration, it may be yellowish.

Compatibility

Cefuroxime sodium (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 hours at 25 °C.

Cefuroxime sodium is compatible with aqueous solutions containing up to 1% lidocaine hydrochloride.

Cefuroxime sodium is compatible with the following infusion fluids. It will retain potency for up to 24 hours at room temperature in:

- 0.9% Sodium Chloride Injection BP w/v
- 5% Dextrose Injection BP
- 0.18% w/v Sodium Chloride plus 4% Dextrose Injection BP
- 5% dextrose containing 0.9% Sodium Chloride Injection
- 5% dextrose containing 0.45% Sodium Chloride Injection
- 5% dextrose containing 0.225% Sodium Chloride Injection
- 10% Dextrose Injection
- 10% Invert Sugar in Water for Injection
- Ringer's injection USP
- Lactated Ringer's Injection USP
- M/6 Sodium Lactate Injection
- Compound Sodium Lactate Injection BP (Hartmann's Solution).

The stability of cefuroxime sodium in Sodium Chloride Injection BP 0.9% w/v and in 5% Dextrose Injection is not affected by the presence of hydrocortisone sodium phosphate.

Cefuroxime sodium has also been found compatible for 24 hours at room temperature when admixed in i.v. infusion with:

Heparin (10 and 50 units/mL) in 0.9% w/v Sodium Chloride Injection; Potassium Chloride (10 and 40 mEqL) in 0.9% w/v Sodium Chloride Injection.

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

7. Marketing authorisation holder

SAKAR Healthcare Limited

Block No. 10-13, Sarkhej-Bavla Highway,

Changodar, Ahmedabad – 382213, Gujarat, India

8. Marketing authorisation number(s)

05558/5115/NMR/2017

9. Date of first authorisation/renewal of the authorisation

16/12/2020

10. Date of revision of the text

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Summary of Product Characteristic

1. Name of the medicinal product

SALEXIN 500 CAPSULE - Cefalexin Capsule BP 500 mg

2. Qualitative and quantitative composition

Each hard gelatin capsules contains:

Cefalexin Monohydrate BP

Eq. to Anhydrous Cefalexin 500 mg

Excipients q.s

Approved colour used in capsule shells

For full list of excipients, see 6.1

3. Pharmaceutical form

Capsules, hard

Size 0 Red/White capsule containing white powder

4. Clinical particulars

4.1 Therapeutic indications

Cefalexin is a semi synthetic cephalosporin antibiotic for oral administration.

Cefalexin is indicated in the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections.

Otitis media.

Skin and soft tissue infections.

Bone and joint infections.

Genito-urinary infections, including acute prostatitis.

Dental infections.

Cefalexin is active against the following organisms in vitro: β -haemolytic streptococci; staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains; Streptococcus pneumoniae; Escherichia coli; Proteus mirabilis; Klebsiella species, Haemophilus influenzae; Branhamella catarrhalis.

Most strains of enterococci (Streptococcus faecalis) and a few strains of staphylococci are resistant to cefalexin. Cefalexin is inactive against most strains of enterobacter, morganela morganii, pr. Vulgaris, Colstridium difficile, and the following species: legionella, campylobacter, pseudomonas or herellea species. When tested by in vitro methods, staphylococci exhibit cross-resistance between cefalexin and methicillin-type antibiotics.

4.2 Posology and method of administration

Posology

Adults

The adult dosage ranges from 1-4 g daily in divided doses; most infections will respond to a dosage of 500 mg every 8 hours. For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the usual dosage is 250 mg every 6 hours, or 500 mg every 12 hours.

For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cefalexin greater than 4g are required parenteral cephalosporins, in appropriate doses, should be considered.

Elderly and patients with impaired renal function:

As for adults although dosage should be reduced to a daily maximum of 500mg if renal function is severely impaired (glomerular filtration rate < 10ml/min) (see section 4.4).

Paediatric population

The recommended daily dosage for children is 25-50mg/kg (10-20mg/lb) in divided doses. For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the total daily dose may be divided and administered every 12 hours. For most infections the following schedule is suggested:

Children under 5 years: 125mg every 8 hours.

Children 5 years and over: 250mg every 8 hours.

In severe infections, the dosage may be doubled. In the therapy of otitis media, clinical studies have shown that a dosage of 75-100mg/kg/day in 4 divided doses is required.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Cefalexin is contraindicated in patients with known allergy to the cephalosporins group of antibiotics or to any of the excipients listed in section 6.1.

Cefalexin should be given cautiously to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Cefalexin is contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Before instituting therapy with cefalexin, every effort should be made to determine whether the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins or other drugs. Cefalexin should be given cautiously to penicillin-sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semisynthetic penicillins and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

If an allergic reaction to cefalexin occurs the drug should be discontinued and the patient treated with the appropriate agents.

Prolonged use of cefalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended. If dialysis is required for renal failure, the daily dose of cefalexin should not exceed 500mg.

Concurrent administration with certain other drug substances, such as aminoglycosides, other cephalosporins, or furosemide, (frusemide) and similar potent diuretics, may increase the risk of nephrotoxicity.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. 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, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

Cefalexin capsule contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-lactam drugs, renal excretion of cephalixin is inhibited by probenecid. Probenecid causes reduced excretion of cefalexin leading to increased plasma concentrations. Cephalosporins may have an increased risk of nephrotoxicity in the presence of amphotericin, loop diuretics, aminoglycosides, capreomycin or vancomycin.

In a single study of 12 healthy subjects given single 500mg doses of cefalexin and metformin, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No side-effects were reported in the 12 healthy subjects in this study. No information is available about the interaction of cefalexin and metformin following multiple dose administration. The clinical significance of this study is unclear, particularly as no cases of “lactic acidosis” have been reported in association with concomitant metformin and cefalexin treatment.

Hypokalaemia has been described in patient taking cytotoxic drugs for leukaemia when they were given gentamicin and cephalixin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing for the pregnant patient.

Breastfeeding

The excretion of cefalexin in human breast milk increased up to 4 hours following a 500mg dose. The drug reached a maximum level of 4 micrograms/ml then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing mother, since the neonate is presented with the risk of candidiasis and CNS toxicity due to immaturity of the blood-brain barrier. There is a theoretical possibility of later sensitisation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Gastro-intestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side-effect has been diarrhoea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity: Allergic reactions have been observed in the form of rash, urticaria, angioedema, rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. These reactions usually subside upon discontinuation of the drug, although in some cases supportive therapy may be necessary. Anaphylaxis has also been reported.

Haemic and Lymphatic System: Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and positive Coombs' test have been reported.

Hepatic: As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely. Slight elevations of AST and ALT have been reported.

Skin and subcutaneous tissue disorders:

Acute generalised exanthematous pustulosis (AGEP) has been reported with unknown frequency.

Other: These have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, fever, arthralgia, arthritis and joint disorder, acute generalised exanthematous pustulosis (AGEP), hyperactivity, nervousness, sleep disturbances and hypertonia. Reversible interstitial nephritis has been reported rarely. Slight elevations in AST and ALT have been observed rarely.

4.9 Overdose

Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhoea and haematuria.

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefalexin. It would be extremely unlikely that one of these procedures would be indicated.

Unless 5 - 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria without impairment of renal function in children accidentally ingesting more than 3.5g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, first generation cephalosporins, ATC code: J01DB01

Cefalexin is bactericidal and has antimicrobial activity similar to that of cephaloridine or cephalothin against both gram-positive and gram-negative organisms.

In vitro tests demonstrate that cephalosporins are bactericidal because of their inhibition of cell-wall synthesis.

Cefalexin is active against the following organisms in vitro:

Beta haemolytic streptococci

Staphylococci, including coagulase positive, coagulase negative and penicillinase-producing strains.

Streptococcus pneumoniae

Escherichia coli

Proteus mirabilis

Klebsiella species

Haemophilus influenzae

Branhamella catarrhalis

Most strains of enterococci (*Streptococcus faecalis*) and a few strains of *staphylococci* are resistant to cefalexin. It is not active against most strains of *Enterobacter species*, *Morganella morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea species* or *Acinetobacter calcoaeticus*. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics. When tested by in vitro methods, staphylococci exhibit cross resistance between cefalexin and methicillin type antibiotics

5.2 Pharmacokinetic properties

Absorption

Human pharmacology - Cefalexin is acid stable and may be given without regard to meals.

It is rapidly absorbed after oral administration from the gastro-intestinal tract and produces peak plasma concentrations about 1 hour after administration. Following doses of 250mg, 500mg and 1g, average peak serum levels of approximately 9, 18 and 32 mg/L respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration.

Cefalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine. If cefalexin is taken with food there is delayed and slightly reduced absorption and there may be delayed elimination from the plasma.

The half-life is approximately 60 minutes in patients with normal renal function. Haemodialysis and peritoneal dialysis will remove cefalexin from the blood.

The biological half-life has been reported to range from 0.6 to at least 1.2 hours and this increases with reduced renal function. About 10 to 15% of a dose is bound to plasma proteins.

Distribution

Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. About 80% of the active drug is excreted in the urine within 6 hours. No accumulation is seen with dosages above the therapeutic maximum of 4g/day.

The half-life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50mg/kg/day.

Elimination

Cefalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period peak urine concentrations following the 250mg, 500mg and 1g doses were approximately 1000, 2200 and 5000mg/L respectively.

5.3 Preclinical safety data

The daily oral administration of cefalexin to rats in doses of 250 or 500mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size.

Cefalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals.

The oral LD₅₀ of cefalexin in rats is 5,000mg/kg.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose (C)

Magnesium Stearate

Empty Hard Gelatin Capsules Size '0' (Red/White)

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store Below 30 °C. Protect from light.

6.5 Nature and contents of container

Red/white size '0' locked hard gelatin capsules containing off white granular powder

6.6 Special precautions for disposal and other handling

No special instructions

7. Marketing authorisation holder

SAKAR Healthcare Limited

Block No. 10-13, Sarkhej-Bavla Highway,

Changodar, Ahmedabad – 382213, Gujarat, India

8. Marketing authorisation number(s)

04852/4828/NMR/2017

9. Date of first authorisation/renewal of the authorisation

24/12/2019

10. Date of revision of the text

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Summary of Product Characteristic

1. Name of the medicinal product

SALEXIN 250 DRY SYRUP - Cefalexin Oral Suspension BP

2. Qualitative and quantitative composition

Each 5 ml reconstituted Suspension contains:

Cefalexin Monohydrate BP

Eq. to Anhydrous Cefalexin 250 mg

Excipients q.s.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dry powder for oral suspension

White to off white coloured, flavoured powder which on constitution forms Orange coloured suspension.

4. Clinical particulars

4.1 Therapeutic indications

Cefalexin is a semi synthetic cephalosporin antibiotic for oral administration.

Cefalexin is indicated in the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections,

Otitis media,

Skin and soft tissue infections,

Bone and joint infections;

Genito-urinary infections, including acute prostatitis

Dental infections.

4.2 Posology and method of administration

Posology

Adults

The adult dosage from 1-4 g daily in divided doses; most infections will respond to a dosage of 500 mg every 8 hours. For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the usual dosage is 250 mg every 6 hours, or 500 mg every 12 hours.

For more severe infections, or those caused by less susceptible organisms larger doses may be needed. If daily doses of cefalexin greater than 4g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Elderly and patients with impaired renal function:

As for adults although dosage should be reduced to a daily maximum of 500mg if renal function is severely impaired (glomerular filtration rate < 10ml/min) (see section 4.4).

Paediatric population

The usual recommended daily dosage for children is 25-50 mg/kg (10-20mg/lb) in divided doses. For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the total daily dose may be divided and administered every 12 hours.

For most infections, the following is suggested:

Children under 5 years: 125mg every 8 hours

Children 5 years and over: 250 mg every 8 hours.

In severe infections, the dosage may be doubled. In the therapy of otitis media, clinical studies have shown that a dosage of 75-100 mg/kg/day in 4 divided doses is required.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

Method of administration

For oral use

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Cefalexin is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics or to any of the excipients listed in section 6.1.

Cefalexin should be given cautiously to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is

some evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Cefalexin is contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Before instituting therapy with cefalexin, every effort should be made to determine whether the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins or other drugs. Cefalexin should be given cautiously to penicillin-sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semisynthetic penicillins and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

If an allergic reaction to cefalexin occurs the drug should be discontinued and the patient treated with the appropriate agents.

Prolonged use of cefalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended. If dialysis is required for renal failure, the daily dose of cefalexin should not exceed 500mg.

Concurrent administration with certain other drug substances, such as aminoglycosides, other cephalosporins, or furosemide (frusemide) and similar potent diuretics, may increase the risk of nephrotoxicity.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics, in haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of new-borns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. 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, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

Cefalexin contains sorbitol:

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Cefalexin contains sodium:

This medicinal product contains 6.50mg sodium per 5ml, equivalent to 0.33% of the WHO recommended maximum daily intake of 2g sodium for an adult.

Cefalexin contains sodium benzoate:

This medicine contains 4.82 mg sodium benzoate in each 5 ml cefalexin oral suspension.

Sodium Benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-lactam drugs, renal excretion of cefalexin is inhibited by probenecid.

In a single study of 12 healthy subjects given single 500mg doses of cefalexin and metformin, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No side-effects were reported in the 12 healthy subjects in this study. No information is available about the interaction of cefalexin and metformin following multiple dose administration. The clinical significance of this study is unclear, particularly as no cases of "lactic acidosis" have been reported in association with concomitant metformin and cefalexin treatment.

Hypokalaemia has been described in patient taking cytotoxic drugs for leukaemia when they were given gentamicin and cephalixin.

4.6 Fertility, pregnancy and lactationPregnancy

Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing for the pregnant patient.

Breastfeeding

The excretion of cefalexin in human breast milk increased up to 4 hours following a 500 mg dose. The drug reached a maximum level of 4 micrograms/ml, then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing woman, since the neonate is presented with the risk of candidiasis and CNS toxicity due to immaturity of the blood-brain barrier. There is a theoretical possibility of later sensitisation.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Gastro-intestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side-effect has been diarrhoea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity: Allergic reactions have been observed in the form of rash, urticaria, angioedema, and rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. These reactions usually subside upon discontinuation of the drug, although in some cases supportive therapy may be necessary. Anaphylaxis has also been reported.

Haemic and Lymphatic System: Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and positive Coombs' tests have been reported.

Skin and subcutaneous tissue disorders:

Not known – Acute generalised exanthematous pustulosis (AGEP) has been reported with unknown frequency.

Other: These have included genital and anal pruritus, genital candidiasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, fever, arthralgia, arthritis and joint disorder and acute generalised exanthematous pustulosis (AGEP). Hyperactivity, nervousness, sleep disturbances and hypertonia have also been reported. Reversible interstitial nephritis has been reported rarely and toxic epidermal necrolysis have been observed rarely. Slight elevations of AST and ALT have been observed.

4.9 Overdose

Symptoms of overdosage may include nausea, vomiting, epigastric distress, diarrhoea and haematuria.

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefalexin. It would be extremely unlikely that one of these procedures would be indicated.

Unless 5 – 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria without impairment of renal function in children accidentally ingesting more than 3.5g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, first-generation cephalosporins, ATC code: J01DB01.

In vitro tests demonstrate that cephalosporins are bactericidal because of their inhibition of cell-wall synthesis.

Cefalexin is active against the following organisms *in vitro*:

Beta-haemolytic streptococci

Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains.

Streptococcus pneumoniae

Escherichia coli

Proteus mirabilis Klebsiella species Haemophilus influenzae Branhamella catarrhalis

Most strains of enterococci (*Streptococcus faecalis*) and a few strains of staphylococci are resistant to cefalexin. It is not active against most strains of *Enterobacter* species, *Morganella morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea species* or *Acinetobacter calcoaceticus*. Penicillin-resistant *Strptococcus pneumonia* is usually cross-resistant to beta- lactam antibiotics. When tested by *in-vitro* methods, staphylococci exhibit cross-resistance between cefalexin and methicillin-type antibiotics.

5.2 Pharmacokinetic properties

Absorption

Cefalexin is acid stable and may be given without regard to meals.

Cefalexin is rapidly absorbed from the gastro-intestinal tract and produces peak plasma concentrations about 1 hour after administration. Following doses of 250mg, 500mg and 1g, average peak serum levels of approximately 9, 18 and 32mg/L respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration. Cefalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period peak urine concentrations following the 250mg, 500mg and 1g doses were approximately 1000, 2200 and 5000mg/L respectively.

Cefalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine.

If cefalexin is taken with food there is delayed and slightly reduced absorption and there may be delayed elimination from the plasma. The half-life is approximately 60 minutes in patients with normal renal function. The biological half-life has been reported to range from 0.6 to at least 1.2 hours and this increases with reduced renal function About 10 to 15% of a dose is bound to plasma proteins. Haemodialysis and peritoneal dialysis will remove cefalexin from the blood.

Distribution

Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. About 80% or more of a dose is excreted unchanged in the urine in the first 6 hours by glomerular filtration and tubular secretion; urinary concentrations greater than 1 mg per ml have been achieved after a dose of 500 mg. Probenecid delays urinary excretion and has been reported to increase biliary excretion. Cefalexin is widely distributed in the body but does not enter the cerebrospinal fluid in significant quantities unless the meninges are inflamed. It diffuses across the placenta and small quantities are found in the milk of nursing mothers. Therapeutically effective concentrations may be found in the bile.

No accumulation is seen with dosages above the therapeutic maximum of 4g/day.

Elimination

Approximately 80% of the active drug is excreted in the urine within 6 hours. No accumulation is seen with dosages above the therapeutic maximum of 4g/day.

The half-life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50mg/kg/day.

5.3 Preclinical safety data

Daily oral administration of cefalexin to rats in doses of 250 or 500mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size.

Cefalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals.

The oral LD₅₀ of cefalexin in rats is 5,000 mg/kg.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Benzoate

Disodium Edetate

Citric Acid (Anhydrous)

Sodium Citrate

Flavour Orange Powder

Colloidal Anhydrous Silica

Carmellose Sodium

Aspartame

Sugar Pharma grade**

Colour Sunset Yellow

Croscarmellose sodium

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Dry Powder: 2 years

Reconstituted Suspension: 14 days

6.4 Special precautions for storage

Store in cool, dry place Below 30 °C. Protect from light.

The re-constituted suspension mixture should be stored in refrigerator (2°C to 8°C)

6.5 Nature and contents of container

Cefalexin Oral Suspension BP (SALEXIN -250 Dry Syrup) is to be packed in 100 ml ring marked Amber Glass Bottle with 25 mm cap & 10 ml measuring cup. Such 1 Bottle is further packed in Printed carton with Package insert

6.6 Special precautions for disposal and other handling

To the Pharmacist:

To prepare, add 87 ml of potable water and shake until powder is dissolved.

The reconstituted solution may be further diluted with sorbitol solution BP, syrup BP or purified water if required.

A pale yellow, free flowing granular powder, which readily disperses in water to give a yellow suspension with an odour of orange.

7. Marketing authorisation holder

SAKAR Healthcare Limited

Block No. 10-13, Sarkhej-Bavla Highway,

Changodar, Ahmedabad – 382213, Gujarat, India

8. Marketing authorisation number(s)

04575/4984/NMR/2017

9. Date of first authorisation/renewal of the authorisation

31/07/2019

10. Date of revision of the text

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1. Name of the medicinal product

SEFIXI 1000 - Ceftriaxone for Injection USP

2. Qualitative and quantitative composition

Each vial contains

Ceftriaxone sodium equivalent to 1g of ceftriaxone.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dry powder for Injection

White to yellowish orange crystalline powder

4. Clinical particulars

4.1 Therapeutic indications

Ceftriaxone is indicated in the treatment of the following infections in adults and children including term neonates (from birth):

Bacterial Meningitis

Community acquired pneumonia

Hospital acquired pneumonia

Acute otitis media

Intra-abdominal infections

Complicated urinary tract infections (including pyelonephritis)

Infections of bones and joints

Complicated skin and soft tissue infections

Gonorrhoea

Syphilis

Bacterial endocarditis

Ceftriaxone may be used:

For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults

For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.

For Pre-operative prophylaxis of surgical site infections

In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection

In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.

The doses recommended in the tables below are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

Adults and children over 12 years of age (≥ 50 kg)

Ceftriaxone Dosage*	Treatment frequency**	Indications
1-2 g	Once daily	Community acquired pneumonia
		Acute exacerbations of chronic obstructive pulmonary disease
		Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Hospital acquired pneumonia
		Complicated skin and soft tissue infections
		Infections of bones and joints
2-4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial endocarditis
		Bacterial meningitis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for adults and children over 12 years of age (≥ 50 kg) that require specific dosage schedules:

Acute otitis media

A single intramuscular dose of Ceftriaxone 1-2 g can be given. Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

Pre-operative prophylaxis of surgical site infections

2 g as a single pre-operative dose.

Gonorrhoea

500 mg as a single intramuscular dose.

Syphilis

The generally recommended doses are 500 mg-1 g once daily increased to 2 g once daily for neurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

2 g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Paediatric population

Neonates, infants and children 15 days to 12 years of age (< 50 kg)

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

Ceftriaxone dosage*	Treatment frequency**	Indications
50-80 mg/kg	Once daily	Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
50-100 mg/kg (Max 4 g)	Once daily	Complicated skin and soft tissue infections
		Infections of bones and joints
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)	Once daily	Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for neonates, infants and children 15 days to 12 years (< 50 kg) that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

Pre-operative prophylaxis of surgical site infections

50-80 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Neonates 0-14 days

Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Ceftriaxone dosage*	Treatment frequency	Indications
20-50 mg/kg	Once daily	Intra-abdominal infections
		Complicated skin and soft tissue infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
		Infections of bones and joints
50 mg/kg	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial meningitis
		Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given.

Pre-operative prophylaxis of surgical site infections

20-50 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.

Older people

The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.

Patients with hepatic impairment

Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

There are no study data in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment:

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

In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Method of administration

Intramuscular administration

1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP. The solution should be administered by deep intramuscular injection.

Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site.

Dosages greater than 1g should be divided and injected at more than one site.

As the solvent used is lidocaine, the resulting solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.

Intravenous administration

For IV injection 1 g ceftriaxone is dissolved in 10 ml of water for injections PhEur. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section 4.3 and 4.4). Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium (see section 4.3).

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

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 agent (penicillins, monobactams and carbapenems).

Ceftriaxone is contraindicated in:

- Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*

- 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-calcium salt (see sections 4.4, 4.8 and 6.2).

* *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.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (see section 4.4). See information in the Summary of Product Characteristics of lidocaine, especially contraindications.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal, have been reported in association with ceftriaxone treatment; however, the frequency of these events is not known (see section 4.8).

Jarisch-Herxheimer reaction (JHR)

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

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone 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 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.

Ceftriaxone 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 (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, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone 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 agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftriaxone (see section 4.8).

Discontinuation of therapy with ceftriaxone and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

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

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 may lead to false-positive test results. Ceftriaxone 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 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

This medicinal product contains 82mg sodium per 1g vial, equivalent to 4.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section 4.2). In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine

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

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with Ceftriaxone (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 (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

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 should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone 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 is mixed with calcium-containing solutions in the same intravenous administration line.

Ceftriaxone 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 and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone (see section 4.8).

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

In an *in-vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

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

In patients treated with ceftriaxone, 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 should be carried out enzymatically.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development (see section 5.3).

Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

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

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100 - < 1/10$)

Uncommon ($\geq 1/1000$ - $< 1/100$)

Rare ($\geq 1/10000$ - $< 1/1000$)

Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known^a
Infections and infestations		Genital fungal infection	Pseudomembranous colitis ^b	Superinfection ^b
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia ^b Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity ^b Jarisch-Herxheimer reaction ^b
Nervous system disorders		Headache Dizziness	Encephalopathy	Convulsion
Ear and labyrinth disorders				Vertigo
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
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome ^b Toxic epidermal necrolysis ^b Erythema multiforme Acute

				generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS) ^b
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site reactions Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive ^b Galactosaemia test false positive ^b Non enzymatic methods for glucose determination false positive ^b

^aBased 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.

^bSee section 4.4

Description of selected adverse reactions

Infections and infestations

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

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

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

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC code: J01DD04

Mechanism of action

Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Resistance

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- reduced affinity of penicillin-binding proteins for ceftriaxone.
- outer membrane impermeability in Gram-negative organisms.
- bacterial efflux pumps.

Susceptibility testing Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	Dilution Test (MIC, mg/L)	
	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤ 1	> 2
<i>Staphylococcus</i> spp	a.	a.
<i>Streptococcus</i> spp. (Groups A, B, C and G)	b.	b.
<i>Streptococcus pneumoniae</i>	≤ 0.5 ^c	> 2
Viridans group <i>Streptococci</i>	≤0.5	>0.5
<i>Haemophilus influenzae</i>	≤ 0.12 ^c	> 0.12
<i>Moraxella catarrhalis</i>	≤ 1	> 2
<i>Neisseria gonorrhoeae</i>	≤ 0.12	> 0.12
<i>Neisseria meningitidis</i>	≤ 0.12 ^c	> 0.12
Non-species related	≤ 1 ^d	> 2

a. Susceptibility inferred from cefoxitin susceptibility.

b. Susceptibility inferred from penicillin susceptibility.

c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.

d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

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.

Commonly susceptible species

Gram-positive aerobes
Staphylococcus aureus (methicillin-susceptible)^ε *Staphylococci*
 coagulase-negative (methicillin-susceptible)^ε *Streptococcus*
pyogenes (Group A)
Streptococcus agalactiae (Group B)
Streptococcus pneumoniae
 Viridans Group *Streptococci*
 Gram-negative aerobes
Borrelia burgdorferi
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoea
Neisseria meningitidis

Proteus mirabilis
Providencia spp
Treponema pallidum

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.

⁺ Resistance rates >50% in at least one region

[%] ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. 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. An 8 - 15 % increase in mean peak plasma concentration (C_{max}) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

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).

Biotransformation

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

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by

glomerular filtration, 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 with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

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

Paediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

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 drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Solutions containing ceftriaxone should not be mixed with or added to other agents 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 vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone 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 is intended, administration should not occur in the same syringe or in the same infusion solution.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store Below 30 °C.

6.5 Nature and contents of container

10 ml flint glass vial with dry sterile powder is packed in a Printed Primary Carton along with the Pack Insert. One ampoule containing 10 ml Sterile Water for Injections BP is included in this pack for reconstitution.

6.6 Special precautions for disposal and other handling

1g vial - Concentrations for the intravenous injection: 100 mg/ml,

1g vial - Concentrations for the intravenous infusion: 50 mg/ml

2g vial – Concentrations for the intravenous injection or intravenous infusion: approximately 50 mg/ml

(Please refer to section 4.2 for further information).

Reconstitution Table

Strength	Administration route	Diluent	Volume of diluent to	Approximate available volume	Approximate displacement
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			be added (ml)	(ml)	volume (ml)
1g	Intravenous injection ¹	Water for injections	10ml	10.8ml	0.8ml
1g	Intramuscular injection	1% lidocaine	3.5ml	4.1ml	0.6ml
2g	Intramuscular injection ²	1% lidocaine	7ml	8.4ml	1.4ml
2g	Intravenous injection or infusion	See list of compatible diluents below*	40ml	41.5ml [#]	1.5ml [#]

¹For Intravenous injection, 1g ceftriaxone is dissolved in 10ml of Water for Injections. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

²Dosages greater than 1g should be divided and injected at more than one site.

[#]These approximate available volume and approximate displacement volume values are when reconstituted using Water for Injections.

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicinal product, see section 6.3.

Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Injection BP (for intramuscular injection only).

*Ceftriaxone is compatible with several commonly used intravenous infusion fluids e.g. Sodium Chloride Intravenous Infusion BP, 5% or 10% Glucose Intravenous Infusion BP, Sodium Chloride and Glucose Intravenous Infusion BP (0.45% sodium chloride and 2.5% glucose), Dextran 6% in Glucose Intravenous Infusion BP 5%, isotonic hydroxyethylstarch 6-10% infusions and Water for Injections.

The reconstituted solution should be clear. Do not use if particles are present.

Ceftriaxone sodium when dissolved in Water for Injections Ph Eur forms a pale yellow to amber solution. Variations in the intensity of colour of the freshly prepared solutions do not indicate a change in potency or safety.

For single use only. Discard any unused contents.

7. Marketing authorisation holder

SAKAR Healthcare Limited

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Changodar, Ahmedabad – 382213, Gujarat, India

8. Marketing authorisation number(s)

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Delivered

Summary of Product Characteristic

1. Name of the medicinal product

SALEXIN 250 CAPSULE - Cefalexin Capsule BP 250 mg

2. Qualitative and quantitative composition

Each hard gelatin capsules contains:

Cefalexin Monohydrate BP

Eq. to Anhydrous Cefalexin 250 mg

Excipients q.s

Approved colour used in capsule shells

For full list of excipients, see 6.1

3. Pharmaceutical form

Capsules, hard

Blue / white size '2' locked hard gelatin capsules containing off white granular Powder.

4. Clinical particulars

4.1 Therapeutic indications

Cefalexin is a semi synthetic cephalosporin antibiotic for oral administration.

Cefalexin is indicated in the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections.

Otitis media.

Skin and soft tissue infections.

Bone and joint infections.

Genito-urinary infections, including acute prostatitis.

Dental infections.

Cefalexin is active against the following organisms in vitro: β -haemolytic streptococci; staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Cefalexin is contraindicated in patients with known allergy to the cephalosporins group of antibiotics or to any of the excipients listed in section 6.1.

Cefalexin should be given cautiously to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Cefalexin is contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Before instituting therapy with cefalexin, every effort should be made to determine whether the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins or other drugs. Cefalexin should be given cautiously to penicillin-sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semisynthetic penicillins and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

If an allergic reaction to cefalexin occurs the drug should be discontinued and the patient treated with the appropriate agents.

Prolonged use of cefalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended. If dialysis is required for renal failure, the daily dose of cefalexin should not exceed 500mg.

Concurrent administration with certain other drug substances, such as aminoglycosides, other cephalosporins, or furosemide, (frusemide) and similar potent diuretics, may increase the risk of nephrotoxicity.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. 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, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

Cefalexin capsule contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-lactam drugs, renal excretion of cephalixin is inhibited by probenecid. Probenecid causes reduced excretion of cefalexin leading to increased plasma concentrations. Cephalosporins may have an increased risk of nephrotoxicity in the presence of amphotericin, loop diuretics, aminoglycosides, capreomycin or vancomycin.

In a single study of 12 healthy subjects given single 500mg doses of cefalexin and metformin, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No side-effects were reported in the 12 healthy subjects in this study. No information is available about the interaction of cefalexin and metformin following multiple dose administration. The clinical significance of this study is unclear, particularly as no cases of “lactic acidosis” have been reported in association with concomitant metformin and cefalexin treatment.

Hypokalaemia has been described in patient taking cytotoxic drugs for leukaemia when they were given gentamicin and cephalixin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing for the pregnant patient.

Breastfeeding

The excretion of cefalexin in human breast milk increased up to 4 hours following a 500mg dose. The drug reached a maximum level of 4 micrograms/ml then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing mother, since the neonate is presented with the risk of candidiasis and CNS toxicity due to immaturity of the blood-brain barrier. There is a theoretical possibility of later sensitisation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Gastro-intestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side-effect has been diarrhoea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity: Allergic reactions have been observed in the form of rash, urticaria, angioedema, rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. These reactions usually subside upon discontinuation of the drug, although in some cases supportive therapy may be necessary. Anaphylaxis has also been reported.

Haemic and Lymphatic System: Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and positive Coombs' test have been reported.

Hepatic: As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely. Slight elevations of AST and ALT have been reported.

Skin and subcutaneous tissue disorders:

Acute generalised exanthematous pustulosis (AGEP) has been reported with unknown frequency.

Other: These have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, fever, arthralgia, arthritis and joint disorder, acute generalised exanthematous pustulosis (AGEP), hyperactivity, nervousness, sleep disturbances and hypertonia. Reversible interstitial nephritis has been reported rarely. Slight elevations in AST and ALT have been observed rarely.

4.9 Overdose

Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhoea and haematuria.

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefalexin. It would be extremely unlikely that one of these procedures would be indicated.

Unless 5 - 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria without impairment of renal function in children accidentally ingesting more than 3.5g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, first generation cephalosporins, ATC code: J01DB01

Cefalexin is bactericidal and has antimicrobial activity similar to that of cephaloridine or cephalothin against both gram-positive and gram-negative organisms.

In vitro tests demonstrate that cephalosporins are bactericidal because of their inhibition of cell-wall synthesis.

Cefalexin is active against the following organisms in vitro:

Beta haemolytic streptococci

Staphylococci, including coagulase positive, coagulase negative and penicillinase-producing strains.

Streptococcus pneumoniae

Escherichia coli

Proteus mirabilis

Klebsiella species

Haemophilus influenzae

Branhamella catarrhalis

Most strains of enterococci (*Streptococcus faecalis*) and a few strains of *staphylococci* are resistant to cefalexin. It is not active against most strains of *Enterobacter species*, *Morganella morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea species* or *Acinetobacter calcoaeticus*. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics. When tested by in vitro methods, staphylococci exhibit cross resistance between cefalexin and methicillin type antibiotics

5.2 Pharmacokinetic properties

Absorption

Human pharmacology - Cefalexin is acid stable and may be given without regard to meals.

It is rapidly absorbed after oral administration from the gastro-intestinal tract and produces peak plasma concentrations about 1 hour after administration. Following doses of 250mg, 500mg and 1g, average peak serum levels of approximately 9, 18 and 32 mg/L respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration.

Cefalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine. If cefalexin is taken with food there is delayed and slightly reduced absorption and there may be delayed elimination from the plasma.

The half-life is approximately 60 minutes in patients with normal renal function. Haemodialysis and peritoneal dialysis will remove cefalexin from the blood.

The biological half-life has been reported to range from 0.6 to at least 1.2 hours and this increases with reduced renal function. About 10 to 15% of a dose is bound to plasma proteins.

Distribution

Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. About 80% of the active drug is excreted in the urine within 6 hours. No accumulation is seen with dosages above the therapeutic maximum of 4g/day.

The half-life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50mg/kg/day.

Elimination

Cefalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period peak urine concentrations following the 250mg, 500mg and 1g doses were approximately 1000, 2200 and 5000mg/L respectively.

5.3 Preclinical safety data

The daily oral administration of cefalexin to rats in doses of 250 or 500mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size.

Cefalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals.

The oral LD₅₀ of cefalexin in rats is 5,000mg/kg.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose (C)

Magnesium Stearate

Empty Hard Gelatin Capsules Size '2' (Blue/White)

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store Below 30 °C. Protect from light.

6.5 Nature and contents of container

Blue/white size '2' locked hard gelatin capsules containing off white granular powder

6.6 Special precautions for disposal and other handling

No special instructions

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

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