

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime sodium 1.5g powder for solution for injection or infusion

Axetine 1.5g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains, as the active ingredient, cefuroxime sodium for injection equivalent to 1.5 g of cefuroxime.

Each vial contains 81.45 mg sodium.

3. PHARMACEUTICAL FORM

Vials containing white or almost white to yellowish powder for solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefuroxime sodium for injection 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		

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.

1.5 g 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 and infusion contains 81.3 mg sodium per of 1.5g vial, equivalent to 4% 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

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 breast-feeding 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).

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		
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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.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

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

Pharmacological classification: 7.2.2 Cephalosporins

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

<p><u>Gram-positive aerobes:</u> <i>Staphylococcus aureus</i> (methicillin-susceptible) § <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i></p>
<p><u>Gram-negative aerobes:</u> <i>Haemophilus parainfluenzae</i> <i>Moraxella catarrhalis</i></p>
<p>Microorganisms for which acquired resistance may be a problem</p>
<p><u>Gram-positive aerobes:</u> <i>Streptococcus pneumoniae</i> <i>Streptococcus mitis</i> (viridans group)</p>
<p><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.</p>
<p><u>Gram-positive anaerobes:</u> <i>Peptostreptococcus</i> spp. <i>Propionibacterium</i> spp.</p>
<p><u>Gram-negative anaerobes:</u> <i>Fusobacterium</i> spp. <i>Bacteroides</i> spp.</p>
<p>Inherently resistant microorganisms</p>
<p><u>Gram-positive aerobes:</u> <i>Enterococcus faecalis</i> <i>Enterococcus faecium</i></p>
<p><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></p>

Gram-positive anaerobes:

Clostridium difficile

Gram-negative anaerobes:

Bacteroides fragilis

Others:

Chlamydia spp.

Mycoplasma spp.

Legionella 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. $Cl_{cr} < 20$ 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

Before reconstitution: 2 years.

Reconstituted Solution: Immediate use of the reconstituted solution is recommended.

Chemical and physical stability has been demonstrated:

- for 5 hours at 30°C and 48 hours at 2°C -8°C (in refrigerator) for the reconstituted solutions for intramuscular or intravenous injection;

- for 6 hours at 30°C and 24 hours at 2°C -8°C (in refrigerator) for the reconstituted solutions for intravenous infusion.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2°C – 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C in its original container.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mL USP type I clear glass vials with grey bromobutyl rubber stoppers and aluminium flip-off seals. Pack size: 10 vials per carton

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
1.5 g	intramuscular intravenous bolus	6 mL at least 15 mL	216 94	Suspension Solution

	intravenous infusion	15 mL*	94	Solution
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* 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 is compatible with the following infusion fluids. It will retain potency for up to 6 hours at 30°C and 24 hours at 2°C -8°C (in refrigerator) in:

- 0.18% w/v Sodium Chloride plus 4% Dextrose Injection BP
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.225% Sodium Chloride Injection
- M/6 Sodium Lactate Injection
- Potassium Chloride (10 and 40 mEqL) in 0.9% Sodium Chloride Injection
- Dextrose (glucose)
- Sodium chloride
- Ringer Solution
- Ringers Lactate

Freshly prepared solution for IV administration is yellowish, while suspension for IM administration is almost white.

Solution can turn darker when standing but change of intensity of color of diluted solution does not affect safety of administration and effectiveness of medicinal product.

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

7. APPLICANT

Cospharm Investments Pty Ltd
ERF 492, Dante Street
Prosperita, Winhoek

Namibia

8. MANUFACTURER

Medochemie Ltd.

Factory C, 2 Michael Erakleous

Street, Agios Athanassios Industrial Area, 4101

Agios Athanassios, Limassol

Cyprus

9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/7.2.2/6403

Category for distribution: Prescription Preparations (P.P.)

10. Date of revision of the text

May 2023