

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zinacef and associated names (see Annex I) 250 mg powder for solution for injection

Zinacef and associated names (see Annex I) 750 mg powder for solution for injection

Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection

Zinacef and associated names (see Annex I) 250 mg powder and solvent for solution for injection

Zinacef and associated names (see Annex I) 500 mg powder and solvent for solution for injection

Zinacef and associated names (see Annex I) 750 mg powder and solvent for solution for injection

Zinacef and associated names (see Annex I) 1 g powder and solvent for solution for injection

Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion

Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion

Zinacef and associated names (see Annex I) 2 g powder for solution for infusion

Zinacef and associated names (see Annex I) 250 mg powder for solution for injection or infusion

Zinacef and associated names (see Annex I) 750 mg powder for solution for injection or infusion

Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection or infusion

Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion (Monovial presentation)

Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion (Monovial presentation)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

<u>Zinacef strength</u>	<u>Amount of sodium per vial</u>
250 mg	14 mg
500 mg	28 mg
750 mg	42 mg
1 g	56 mg
1.5 g	83 mg
2 g	111 mg

3. PHARMACEUTICAL FORM

250 mg, 750 mg, 1.5 g powder for solution for injection

Powder for solution for injection

[To be completed nationally]

250 mg, 500 mg, 750 mg, 1 g powder and solvent for solution for injection

Powder and solvent for solution for injection

[To be completed nationally]

250 mg, 750 mg, 1.5 g powder for solution for injection or infusion

Powder for solution for injection or infusion

[To be completed nationally]

750 mg, 1.5 g, 2 g powder for solution for infusion

Powder for solution for infusion

[To be completed nationally]

750 mg, 1.5 g powder for solution for infusion (Monovial presentation)
Powder for solution for infusion
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zinacef is indicated for the treatment of the 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 < 40kg

	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 Zinacef should be reduced to compensate for its slower excretion.

Table 3. Recommended doses for Zinacef 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

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

750 mg, 1.5 g powder for solution for infusion (Monovial presentation).

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. 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.

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 Coomb's 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.

Important information about excipients

Zinacef powder for solution for injection and infusion contains sodium. 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 the antibiotic 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). Zinacef 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 Coomb's test	thrombocytopenia, haemolytic anaemia
<u>Immune system disorders</u>			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
<u>Gastrointestinal disorders</u>		gastrointestinal disturbance	pseudomembranous colitis
<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
<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 Coomb's 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.

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>S</u>	<u>R</u>
<i>Enterobacteriaceae</i> ¹	≤8 ²	>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
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 strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for 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 methicillin susceptibility except for ceftazidime and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.

⁴ The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

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

S=susceptible, R=resistant.

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> <i>Streptococcus mitis</i> (viridans group)
<u>Gram-negative aerobes:</u> <i>Haemophilus influenzae</i> <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>
<u>Gram-negative aerobes:</u> <i>Citrobacter freundii</i> <i>Enterobacter cloacae</i> <i>Enterobacter aerogenes</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Proteus</i> spp. (other than <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>Morganella morganii</i> <i>Proteus vulgaris</i> <i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i>
<u>Gram-positive anaerobes:</u> <i>Clostridium difficile</i>
<u>Gram-negative anaerobes:</u> <i>Bacteroides fragilis</i>

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 injection 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

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Instructions for constitution

Table 4. Addition volumes and solution concentrations, which may be useful when fractional doses are required.

Addition volumes and solution concentrations, which may be useful when fractional doses are required			
<u>Vial size</u>		<u>Amount of water to be added (ml)</u>	Approximate cefuroxime concentration (mg/mL)**
250 mg powder for solution for injection			
250 mg	intramuscular	1 mL	216
	intravenous	at least 2 mL	116
500 mg powder for solution for injection			
500 mg	intramuscular	2 mL	216
750 mg powder for solution for injection or infusion			
750 mg	intramuscular	3 mL	216
	intravenous bolus	at least 6 mL	116
	intravenous infusion	at least 6 mL	116
1 g powder for solution for injection			
1 g	intramuscular	4 mL	216
	intravenous bolus	10 mL	94
1.5 g powder for solution for injection or infusion			
1.5 g	intramuscular	6 mL	216
	intravenous bolus	at least 15mL	94
	intravenous infusion	15 mL*	94
2 g powder for solution for infusion			
2 g	intravenous infusion	20 mL	94

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

Zinacef 750 mg and 1.5 g powder for solution for infusion (Monovial presentation)

Preparation of solution for intravenous infusion

The contents of the Monovial are added to small volume infusion bags containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or another compatible fluid.

1. Peel off the removable top part of the label and remove the cap.
2. Insert the needle of the Monovial into the additive port of the infusion bag.
3. To activate, push the plastic needle holder of the Monovial down onto the vial shoulder until a "click" is heard.
4. Holding it upright, fill the vial to approximately two-thirds capacity by squeezing the bag several times.
5. Shake the vial to reconstitute the cefuroxime sodium.
6. With the vial uppermost, transfer the reconstituted cefuroxime sodium into the infusion bag by squeezing and releasing the bag.
7. Repeat steps 4 to 6 to rinse the inside of the vial. Dispose of the empty Monovial safely. Check that the powder has dissolved, and that the bag has no leaks.

Compatibility

1.5 g cefuroxime sodium constituted with 15 mL Water for Injection may be added to metronidazole injection (500 mg/100 ml) and both retain their activity for up to 24 hours below 25 °C.

1.5 g cefuroxime sodium is compatible with azlocillin 1 g (in 15 ml) or 5 g (in 50 ml) for up to 24 h at 4°C or 6 h below 25°C.

Cefuroxime sodium (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 h 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:

- Sodium Chloride Injection BP 0.9% w/v
- 5% Dextrose Injection BP
- 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
- 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 h at room temperature when admixed in i.v. infusion with:

- Heparin (10 and 50 units/ml) in 0.9% Sodium Chloride Injection; Potassium Chloride (10 and 40 mEqL) in 0.9% Sodium Chloride Injection.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and address}

<{tel}>

<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zinacef and associated names (see Annex I) 250 mg powder for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection
Zinacef and associated names (see Annex I) 250 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 500 mg powder and solvent for solution for injection
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Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion
Zinacef and associated names (see Annex I) 2 g powder for solution for infusion
Zinacef and associated names (see Annex I) 250 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion (Monovial presentation)
Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion (Monovial presentation)

[See Annex I - To be completed nationally]

Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Zinacef 250 mg , 750 mg and 1.5 g powder for solution for injection;
Zinacef 250 mg, 750 mg and 1.5 g powder for solution for injection or infusion
Intramuscular or intravenous use.

Zinacef 250 mg, 500 mg, 750 mg and 1 g powder and solvent for solution for injection
Intramuscular or intravenous use.

Zinacef 750 mg, 1.5 g and 2 g powder for solution for infusion
Intravenous use.

Zinacef 750 mg and 1.5 g powder for solution for infusion (Monovial presentation)
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zinacef and associated names (see Annex I) 250 mg powder for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection
Zinacef and associated names (see Annex I) 250 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 500 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 1 g powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion
Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion
Zinacef and associated names (see Annex I) 2 g powder for solution for infusion
Zinacef and associated names (see Annex I) 250 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion (Monovial presentation)
Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion (Monovial presentation)

Cefuroxime

Zinacef 250 mg , 750 mg and 1.5 g powder for solution for injection;
Zinacef 250 mg, 750 mg and 1.5 g powder for solution for injection or infusion
IM/IV.

Zinacef 250 mg, 500 mg, 750 mg and 1 g powder and solvent for solution for injection
IM/IV

Zinacef 750 mg, 1.5 g and 2 g powder for solution for infusion
IV

Zinacef 750 mg and 1.5 g powder for solution for infusion (Monovial presentation)
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
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[To be completed nationally]

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Zinacef and associated names (see Annex I) 250 mg powder for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection
Zinacef and associated names (see Annex I) 250 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 500 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 1 g powder and solvent for solution for injection
Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion
Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion
Zinacef and associated names (see Annex I) 2 g powder for solution for infusion
Zinacef and associated names (see Annex I) 250 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 1.5 g powder for solution for injection or infusion
Zinacef and associated names (see Annex I) 750 mg powder for solution for infusion (Monovial presentation)
Zinacef and associated names (see Annex I) 1.5 g powder for solution for infusion (Monovial presentation)

Cefuroxime

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Zinacef is and what it is used for
2. What you need to know before you are given Zinacef
3. How Zinacef is given
4. Possible side effects
5. How to store Zinacef
6. Contents of the pack and other information

1. What Zinacef is and what it is used for

Zinacef is an antibiotic used in adults and children. It works by killing bacteria that cause infections. It belongs to a group of medicines called *cephalosporins*.

Zinacef is used to treat infections of:

- the lungs or chest
- the urinary tract
- the skin and soft tissue
- the abdomen

Zinacef is also used:

- to prevent infections during surgery.

2. What you need to know before you are given Zinacef

You must not be given Zinacef:

- if you are allergic (*hypersensitive*) to any cephalosporin antibiotics or any of the other ingredients of Zinacef .
- if you have ever had a severe allergic (*hypersensitive*) reaction to any other type of betalactam antibiotic (penicillins, monobactams and carbapenems).

➔ **Tell your doctor before** you start on Zinacef if you think that this applies to you. You must not be given Zinacef.

Take special care with Zinacef

You must look out for certain symptoms such as allergic reactions and gastrointestinal disorders such as diarrhoea while you are being given Zinacef. This will reduce the risk of possible problems. See (*‘Conditions you need to look out for’*) in section 4. If you have had any allergic reaction to other antibiotics such as penicillin, you may also be allergic to Zinacef.

If you need a blood or urine test

Zinacef can affect the results of urine or blood tests for sugar and a blood test known as the *Coombs test*.

If you are having tests:

➔ **Tell the person taking the sample** that you have been given Zinacef.

Other medicines and Zinacef

Tell your doctor if you are taking any other medicines, if you’ve started taking any recently or you start taking new ones. This includes medicines you can obtain without a prescription.

Some medicines may affect how Zinacef works, or make it more likely that you’ll have side effects. These include:

- **aminoglycoside-type antibiotics**
 - **water tablets** (diuretics), such as furosemide
 - **probenecid**
 - **oral anticoagulants**
- ➔ **Tell your doctor** if this applies to you. You may need extra check-ups to monitor your renal function while you are taking Zinacef.

Contraceptive pills

Zinacef may reduce the effectiveness of the contraceptive pill. If you are taking the contraceptive pill while you are being treated with Zinacef you also need to use a **barrier method of contraception** (such as condoms). Ask your doctor for advice.

Pregnancy and breast-feeding and fertility

Tell your doctor before you are given Zinacef:

- if you are pregnant, think you might be pregnant or are planning to become pregnant
- if you are breastfeeding

Your doctor will consider the benefit of treating you with Zinacef against the risk to your baby.

Driving and using machines

Don’t drive or use machines if you do not feel well.

Important information about some of the ingredients of Zinacef

Zinacef contains sodium. You need to take this into account if you are on a controlled sodium diet.

<u>Zinacef strength</u>	<u>Amount per vial</u>
250 mg	14 mg
500 mg	28 mg
750 mg	42 mg
1 g	56 mg
1.5 g	83 mg
2 g	111 mg

3. How Zinacef is given

Zinacef is usually be given by a doctor or nurse. It can be given as a **drip** (intravenous infusion) or as an **injection** directly into a vein or into a muscle.

The usual dose

The correct dose of Zinacef for you will be decided by your doctor and depends on: the severity and type of infection, whether you are on any other antibiotics; your weight and age; how well your kidneys are working.

Newborn babies (0 - 3 weeks)

For every 1 kg the baby weighs, they'll be given 30 to 100 mg Zinacef per day divided in two or three doses.

Babies (over 3 weeks) and children

For every 1 kg the baby or child weighs, they'll be given 30 to 100 mg of Zinacef per day divided in three or four doses.

Adults and adolescents

750 mg to 1.5 g of Zinacef per day divided into two, three or four doses. Maximum dose: 6 g per day.

Patients with kidney problems

If you have a kidney problem, your doctor may change your dose.

➔ **Talk to your doctor** if this applies to you.

4. Possible side effects

Like all medicines, Zinacef can cause side effects, although not everybody gets them.

Conditions you need to look out for

A small number of people taking Zinacef get an allergic reaction or potentially serious skin reaction. Symptoms of these reactions include:

- **severe allergic reaction.** Signs include **raised and itchy rash, swelling**, sometimes of the face or mouth causing **difficulty in breathing**.
- **skin rash**, which may **blister**, and looks like **small targets** (central dark spot surrounded by a paler area, with a dark ring around the edge).
- **a widespread rash with blisters and peeling skin.** (These may be signs of *Stevens-Johnson syndrome* or *toxic epidermal necrolysis*).

- **fungal infections** on rare occasions, medicines like Zinacef can cause an overgrowth of yeast (*Candida*) in the body which can lead to fungal infections (such as thrush). This side effect is more likely if you take Zinacef for a long time.
- ➔ **Contact a doctor or nurse immediately if you get any of these symptoms.**

Common side effects

These may affect **up to 1 in 10 people:**

- injection site pain, swelling and redness along a vein.
- ➔ **Tell your doctor** if any of these are troubling you.

Common side effects that may show up in blood tests:

- increases in substances (*enzymes*) produced by the liver
- changes in your white blood cell count (*neutropenia* or *eosinophilia*)
- low levels of red blood cells (*anaemia*)

Uncommon side effects

These may affect **up to 1 in 100 people:**

- skin rash, itchy, bumpy rash (*hives*)
 - diarrhoea, nausea, stomach pain
- ➔ **Tell your doctor** if you get any of these.

Uncommon side effects that may show up in blood tests:

- low levels of white blood cells (*leucopenia*)
- increase in bilirubin (a substance produced by the liver)
- positive Coomb's test.

Other side effects

Other side effects have occurred in a very small number of people but their exact frequency is unknown:

- fungal infections
 - high temperature (*fever*)
 - allergic reactions
 - inflammation of the colon (large intestine), causing diarrhoea, usually with blood and mucus, stomach pain
 - inflammation in the kidney and blood vessels
 - red blood cells destroyed too quickly (*haemolytic anaemia*).
 - skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler area, with a dark ring around the edge) *erythema multiformae*.
- ➔ **Tell your doctor** if you get any of these.

Side effects that may show up in blood tests:

- decrease in number of blood platelets (cells that help blood to clot - *thrombocytopenia*)
- increase in levels of urea nitrogen and serum creatinine in the blood.

5 If you get any side effects

→ **Tell your doctor or pharmacist.** This includes any possible side effects not listed in this leaflet.

5. How to store Zinacef

[To be completed nationally]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

Don't throw away any medicines via wastewater or household waste. Your doctor or nurse will dispose of any medicine that is no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zinacef contains

[To be completed nationally]

What Zinacef looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

250 mg powder for solution for injection

Austria – Curocef

Denmark, Finland, Greece, Hungary, Ireland, Lithuania, Malta, Netherlands, Norway, Poland, Sweden,
United Kingdom – Zinacef

Italy – Curoxim

France - Zinnat

500 mg powder for solution for injection

Italy – Curoxim

750 mg powder for solution for injection or infusion

Austria – Curocef

Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Iceland,
Ireland, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia,
Sweden, United Kingdom – Zinacef

Italy – Curoxim

France - Zinnat

1 g powder for solution for injection or infusion

Italy – Curoxim

1.5 g powder for solution for injection or infusion

Austria – Curocef

Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Lithuania, Luxembourg, Netherlands, Norway, Poland, Romania, Slovenia, Sweden, United Kingdom – Zinacef

France - Zinnat

2 g powder for solution for infusion

Italy – Curoxim

750 mg Monovial powder for solution for infusion

Italy – Curoxim

1.5 g Monovial powder for solution for infusion

Belgium, Luxembourg – Zinacef

Italy – Curoxim

This leaflet was last approved in {MM/YYYY}.

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The following information is intended for medical or healthcare professionals only:

Instructions for reconstitution

Addition volumes and solution concentrations, which may be useful when fractional doses are required.

Addition volumes and solution concentrations, which may be useful when fractional doses are required			
<u>Vial size</u>		<u>Amount of water to be added (ml)</u>	Approximate cefuroxime concentration (mg/mL)**
250 mg powder for solution for injection			
250 mg	intramuscular	1 mL	216
	intravenous	at least 2 mL	116
500 mg powder for solution for injection			
500 mg	intramuscular	2 mL	216
750 mg powder for solution for injection or infusion			
750 mg	intramuscular	3 mL	216
	intravenous bolus	At least 6 mL	116
	intravenous infusion	At least 6 mL	116
1 g powder for solution for injection			
1 g	intramuscular	4 mL	216
	intravenous bolus	10 mL	94
1.5 g powder for solution for injection or infusion			
1.5 g	intramuscular	6 mL	216
	intravenous bolus	at least 15 mL	94
	intravenous infusion	15 mL*	94
2 g powder for solution for infusion			
2 g	intravenous infusion	20 mL	94

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

Zinacef 750 mg and 1.5 g powder for solution for infusion (Monovial presentation)

Preparation of solution for intravenous infusion

The contents of the Monovial are added to small volume infusion bags containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or another compatible fluid.

1. Peel off the removable top part of the label and remove the cap.
2. Insert the needle of the Monovial into the additive port of the infusion bag.
3. To activate, push the plastic needle holder of the Monovial down onto the vial shoulder until a "click" is heard.
4. Holding it upright, fill the vial to approximately two-thirds capacity by squeezing the bag several times.
5. Shake the vial to reconstitute the cefuroxime sodium.
6. With the vial uppermost, transfer the reconstituted cefuroxime sodium into the infusion bag by squeezing and releasing the bag.
7. Repeat steps 4 to 6 to rinse the inside of the vial. Dispose of the empty Monovial safely. Check that the powder has dissolved, and that the bag has no leaks.

Compatibility

1.5 g cefuroxime sodium constituted with 15 mL Water for Injection may be added to metronidazole injection (500 mg/100 ml) and both retain their activity for up to 24 hours below 25 °C.

1.5 g cefuroxime sodium is compatible with azlocillin 1 g (in 15 ml) or 5 g (in 50 ml) for up to 24 h at 4°C or 6 h below 25°C.

Cefuroxime sodium (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 h 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:

- Sodium Chloride Injection BP 0.9% w/v
- 5% Dextrose Injection BP
- 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
- 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 h at room temperature when admixed in i.v. infusion with:

- Heparin (10 and 50 units/ml) in 0.9% Sodium Chloride Injection; Potassium Chloride (10 and 40 mEqL) in 0.9% Sodium Chloride Injection.