Cefuroxime sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION
ZINACEF Injection contains 250 mg, 750 mg, 1 g and 1.5 g of cefuroxime (as cefuroxime sodium).
ZINACEF MONOVIAL™ contains 750 mg and 1.5 g of cefuroxime (as cefuroxime sodium).

PHARMACEUTICAL FORM
Powder for solution for injection (Injection)
Powder for solution for infusion (MONOVIAL)

CLINICAL PARTICULARS
Indications
ZINACEF is a bactericidal cephalosporin antibiotic which is resistant to most β-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms.

It is indicated for the treatment of infections before the infecting organism has been identified or when caused by sensitive bacteria.

Indications include:
- respiratory tract infections for example, acute and chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess and post-operative chest infections
- ear, nose and throat infections for example, sinusitis, tonsillitis, pharyngitis and otitis media
- urinary tract infections for example, acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria
- soft-tissue infections for example, cellulitis, erysipelas and wound infections
- bone and joint infections for example, osteomyelitis and septic arthritis
- obstetric and gynaecological infections, pelvic inflammatory diseases
- gonorrhoea particularly when penicillin is unsuitable
- other infections including septicaemia, meningitis and peritonitis
- prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery where there is increased risk from infection.

Usually ZINACEF will be effective alone, but when appropriate it may be used in combination with an aminoglycoside antibiotic, or in conjunction with metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynaecological surgery.

ZINACEF is also available as the axetil ester (ZINNAT™) for oral administration. This permits the use of sequential therapy with the same antibiotic, when a change from parenteral to oral therapy is clinically indicated. Where appropriate ZINACEF is effective when used prior to oral therapy with ZINNAT (cefuroxime axetil) in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

Dosage and Administration
ZINACEF Injection is for iv and/or im administration.
ZINACEF MONOVIAL is for iv infusion only.
GENERAL DOSING RECOMMENDATIONS
• Adults
Many infections respond to 750 mg three times daily by i.m. or i.v. injection. For more severe infections the dose should be increased to 1.5 g three times daily given i.v.. The frequency of administration may be increased to 6-hourly if necessary, giving total daily doses of 3 to 6 g. Where clinically indicated, some infections respond to 750 mg or 1.5 g twice daily (i.v. or i.m.) followed by oral therapy with ZINNAT.
• Infants and Children
30 to 100 mg/kg/day given as 3 or 4 divided doses. A dose of 60 mg/kg/day is appropriate for most infections.
• Neonates
30 to 100 mg/kg/day given as 2 or 3 divided doses.
(see Pharmacokinetics).

GONORRHOEA
• Adults
1.5 g as a single dose (as 2 x 750 mg injections
given i.m. with different sites, e.g. each buttock).

MENINGITIS
ZINACEF is suitable for sole therapy of bacterial
meningitis due to sensitive strains.
• Adults: 3 g given i.v. every eight hours.
• Infants and Children: 150 to 250 mg/kg/day given
i.v. in 3 or 4 divided doses
• Neonates: the dosage should be 100 mg/kg/day
given i.v.

PROPHYLAXIS
The usual dose is 1.5 g given i.v. with induction of
anaesthesia for abdominal, pelvic and orthopaedic
operations. This may be supplemented with two
750 mg i.m. doses eight and sixteen hours later.
In cardiac, pulmonary, oesophageal and vascular opera-
tions, the usual dose is 1.5 g given i.v. with induction
of anaesthesia, continuing with 750 mg given i.m. three
times daily for a further 24 to 48 hours.
In total joint replacement, 1.5 g ZINACEF powder
may be mixed dry with each pack of methyl meth-
acrylate cement polymer before adding the liquid
monomer.

SEQUENTIAL THERAPY
• Adults
Duration of both parenteral and oral therapy is
determined by the severity of the infection and the
clinical status of the patient.

Pneumonia
1.5 g ZINACEF three times daily or twice daily
(given i.v. or i.m.) for 48 to 72 hours, followed by
500 mg twice daily ZINNAT (cefuroxime axetil) oral
therapy for 7 to 10 days.

Acute exacerbations of chronic bronchitis
750 mg ZINACEF three times daily or twice daily
(given i.v. or i.m.) for 48 to 72 hours, followed by
500 mg twice daily ZINNAT (cefuroxime axetil) oral
therapy for 7 to 10 days.

RENAL IMPAIRMENT
Cefuroxime is 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 compen-
sate for its slower excretion.
It is not necessary to reduce the standard dose
(750 mg - 1.5 g three times daily) until the creatinine
clearance falls to 20 ml/min or below.
In adults with marked impairment (creatinine clear-
ance 10 - 20 ml/min) 750 mg twice daily is recom-
manded and with severe impairment (creatinine clear-
ance <10 ml/min) 750 mg once daily is adequate.
For patients on haemodialysis a further 750 mg dose
should be given i.v. or i.m. at the end of each dialy-
sis. In addition to parenteral use, ZINACEF can be
incorporated into the peritoneal dialysis fluid (usually
250 mg for every 2 litres of dialysis fluid).
For patients in renal failure on continuous arterio-
ous haemodialysis or high-flux haemofiltration in
intensive therapy units a suitable dosage is 750 mg
twice daily. For low-flux haemofiltration follow the dos-
age recommended under impaired renal function.

Contraindications
Hypersensitivity to cephalosporin antibiotics.

Warnings and Precautions
Special care is indicated in patients who have expe-
rienced an allergic reaction to penicillins or other
beta-lactams.
Cephalosporin antibiotics at high dosage should be
given with caution to patients receiving concurrent
treatment with potent diuretics such as frusemide
or aminoglycosides, as renal impairment has been
reported with these combinations. Renal function
should be monitored in these patients, the elderly,
and those with pre-existing renal impairment (see
Dosage and Administration).
As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few paediatric patients treated with ZINACEF.

Persistence of positive CSF cultures of Haemophilus influenzae at 18-36 hours has also been noted with ZINACEF injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

As with other antibiotics, use of ZINACEF may result in the overgrowth of Candida.

Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. enterococci and Clostridium difficile), which may require interruption of treatment.

With a sequential therapy regime the timing of change to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved. If there is no clinical improvement within 72 hours, then the parenteral course of treatment must be continued.

Please refer to the relevant prescribing information for ZINNAT before initiating sequential therapy.

Interactions
In common with other antibiotics, ZINACEF may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

ZINACEF does not interfere in enzyme-based tests for glycosuria.

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.

It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving ZINACEF.

This antibiotic does not interfere in the alkaline picrate assay for creatinine.

Pregnancy and Lactation
There is no experimental evidence of embryopathic or teratogenic effects attributable to ZINACEF, but, as with all drugs, it should be administered with caution during the early months of pregnancy. Cefuroxime is excreted in human milk, and consequently caution should be exercised when ZINACEF is administered to a nursing mother.

Effects on Ability to Drive and Use Machines
None reported.

Adverse Reactions
Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

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 ZINACEF may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/1000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

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

very common: ≥1 in 10
common: ≥1 in 100 and <1 in 10
uncommon: ≥1 in 1,000 and <1 in 100
rare: ≥1 in 10,000 and <1 in 1,000
very rare: <1/10,000.

Infections and infestations
Rare: Candida overgrowth

Blood and lymphatic system disorders
Common: Neutropenia, eosinophilia.
Uncommon: Leukopenia, decreased haemoglobin concentration, positive Coomb’s test.
Rare: Thrombocytopenia.
Very rare: Haemolytic anaemia.

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.

**Immune system disorders**

**Hypersensitivity reactions including**

Uncommon: Skin rash, urticaria and pruritus.

Rare: Drug fever.

Very rare: Interstitial nephritis, anaphylaxis, cutaneous vasculitis.

See also Skin and subcutaneous tissue disorders and Renal and urinary disorders.

**Gastrointestinal disorders**

Uncommon: Gastrointestinal disturbance.

Very rare: Pseudomembranous colitis.

**Hepatobiliary disorders**

Common: Transient rise in liver enzymes.

Uncommon: Transient rise in bilirubin.

Transient rises in serum liver enzymes or bilirubin occur, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver.

**Skin and subcutaneous tissue disorders**

Very rare: Erythema multiforme, toxic epidermal necrolysis and Stevens Johnson Syndrome.

See also Immune system disorders.

**Renal and urinary disorders**

Very rare: Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (See Warnings and Precautions).

See also Immune system disorders.

**General disorders and administration site conditions**

Common: Injection site reactions which may include pain and thrombophlebitis.

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

**Overdose**

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

Cefuroxime is a well characterised and effective antibacterial agent which has bactericidal activity against a wide range of common pathogens, including β-lactamase producing strains. Cefuroxime has good stability to bacterial β-lactamase, and consequently is active against many ampicillin-resistant or amoxycillin-resistant strains.

The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins.

**ZINACEF** is usually active against the following organisms in vitro.

**Aerobes Gram-negative**

- Escherichia coli
- Klebsiella spp.
- Proteus mirabilis
- Providencia spp.
- Proteus rettgeri
- Haemophilus influenzae (including ampicillin-resistant strains)
- Haemophilus parainfluenzae (including ampicillin-resistant strains)
- Moraxella (Branhamella) catarrhalis
- Neisseria gonorrhoeae (including penicillinase and non-penicillinase producing strains)
- Neisseria meningitidis
- Salmonellae spp. Aerobes Gram-positive
- Staphylococcus aureus and Staphylococcus epidermidis (including penicillinase producing strains but excluding methicillin resistant strains)
- Streptococcus pyogenes (and other β-haemolytic streptococci)
- Streptococcus pneumoniae
- Streptococcus Group B (Streptococcus agalactiae)
- Streptococcus mitis (viridans group)
- Bordetella pertussis

**Anaerobes**

- Gram-positive and Gram-negative cocci (including
Peptococcus and Peptostreptococcus species)  
Gram-positive bacilli (including most Clostridium species)  
Gram-negative bacilli (including Bacteroides and Fusobacterium species)  
Propionibacterium spp.  
Other organisms  
Borrelia burgdorferi.  

The following organisms are not susceptible to ZINACEF:  
- Clostridium difficile  
- Pseudomonas spp.  
- Campylobacter spp.  
- Acinetobacter calcoaceticus  
- Listeria monocytogenes  
- Methicillin resistant strains of Staphylococcus aureus  
- Methicillin resistant strains of Staphylococcus epidermidis  
- Legionella spp.  

Some strains of the following genera are not susceptible to ZINACEF  
- Enterococcus (Streptococcus) faecalis  
- Morganella morganii  
- Proteus vulgaris  
- Enterobacter spp.  
- Citrobacter spp.  
- Serratia spp.  
- Bacteroides fragilis.  

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

**Pharmacokinetics**  
Peak levels of cefuroxime are achieved within 30 to 45 minutes after i.m. administration.  
Protein binding has been variously stated as 33 - 50% depending on the methodology used.  
Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.  

Cefuroxime is not metabolised and is excreted by glomerular filtration and tubular secretion.  
The serum half-life after either i.m. or i.v. injection is approximately 70 minutes.  
In the first weeks of life the serum half-life of cefuroxime can be 3 to 5 times that in the adult.  
Concurrent administration of probenicid prolongs the excretion of the antibiotic and produces an elevated peak serum level.  
There is an almost complete recovery (85-90%) of unchanged cefuroxime in urine within 24 hours of administration. The major part is excreted in the first six hours.  
Serum levels of cefuroxime are reduced by dialysis.  

**Pre-clinical Safety Data**  
No additional data of relevance.  

**PHARMACEUTICAL PARTICULARS**  
**List of Excipients**  
None.  
Each 750 mg vial contains 42 mg sodium (1.8 mEq).  

**Incompatibilities**  
ZINACEF should not be mixed in the syringe with aminoglycoside antibiotics.  
The pH of 2.74% w/v Sodium Bicarbonate Injection BP considerably affects the colour of the solution and therefore this solution is not recommended for the dilution of ZINACEF. However, if required, for patients receiving Sodium Bicarbonate Injection by infusion ZINACEF may be introduced into the tube of the giving set.  

**Shelf Life**  
The expiry date of the powder is indicated on the packaging.  
Reconstituted suspensions of ZINACEF for i.m. injection and aqueous solutions for direct i.v. injection retain their potency for five hours if kept below 25°C and for 48 hours if refrigerated.  

**Special Precautions for Storage**  
Protect from light.  
Some increase in the colour of prepared solutions and suspensions of ZINACEF may occur on storage.
Nature and Contents of Container
As registered locally.

Instructions for Use/Handling
Intramuscular
Add 1 ml Water for Injections to 250 mg ZINACEF or 3 ml Water for Injections to 750 mg ZINACEF. Shake gently to produce an opaque suspension.

Intravenous
Dissolve ZINACEF in Water for Injections using at least 2 ml for 250 mg, at least 6 ml for 750 mg, or 15 ml for 1.5 g.

Intravenous infusion
Dissolve 1.5 g of ZINACEF in 15 ml of Water for Injections. Add the reconstituted solution of ZINACEF to 50 or 100 ml of a compatible infusion fluid (see information on Compatibility below). These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids.

Preparation of solution for intravenous infusion using ZINACEF MONOVIAL
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 (see Pharmaceutical Particulars, Compatibility below).
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 ZINACEF.
6. With the vial uppermost, transfer the reconstituted ZINACEF 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 ZINACEF constituted with 15 ml Water for Injections 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 ZINACEF is compatible with azlocillin 1 g (in 15 ml) or 5 g (in 50 ml) for up to 24 hours at 4°C or 6 hours below 25°C.
ZINACEF (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 hours at 25°C.
ZINACEF is compatible with aqueous solutions containing up to 1% lignocaine hydrochloride.
ZINACEF is compatible with the more commonly used i.v. 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 ZINACEF in Sodium Chloride Injection BP 0.9% w/v and in 5% Dextrose Injection is not affected by the presence of hydrocortisone sodium phosphate.
ZINACEF 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% Sodium Chloride Injection; Potassium Chloride (10 and 40 mEq/L) in 0.9% Sodium Chloride Injection.
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