Zinacef
Cefuroxime sodium

F5381159

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).

CLINICAL INFORMATION

Indications
ZINACEF is a bactericidal cephalosporin antibiotic which is resistant to most beta-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. Susceptibility to *ZINACEF* will vary with geography and time and local susceptibility data should be consulted where available (*see Pharmacological properties, Pharmacodynamics*).
Indications include:
- respiratory tract infections for example, acute exacerbation of 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.
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
Pharmaceutical forms:
ZINACEF Injection: Powder for suspension or solution for injection and Powder for solution for infusion
ZINACEF MONOVIAL: Powder for solution for infusion
ZINACEF Injection is for intravenous (i.v.) and/or intramuscular (i.m.) administration only.
ZINACEF MONOVIAL is for i.v. infusion only.
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.
No more than 750 mg should be injected at one intramuscular site.

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 8 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 8 and 16 hours later.
In cardiac, pulmonary, oesophageal and vascular operations, 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 methacrylate 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 to10 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 5 to10 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 compensate for its slower excretion.
It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily) until the creatinine clearance falls to 20 ml/min or below.
In adults with marked impairment (creatinine clearance 10 to 20 ml/min) 750 mg twice daily is recommended and with severe impairment (creatinine clearance <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 dialysis. 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 arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units a suitable dosage is 750 mg twice daily. For low-flux haemofiltration follow the dosage recommended under impaired renal function.

Contraindications
Hypersensitivity to cephalosporin antibiotics.

Warnings and Precautions
Special care is indicated in patients who have experienced 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 furosemide 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 cerebral spinal fluid (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 *Clostridioides difficile*), which may require interruption of treatment.
Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.
Intracameral use and ocular toxicity
Serious ocular toxicity, including corneal opacity, retinal toxicity and visual impairment has been reported following off-label intracameral use of *ZINACEF. ZINACEF* should not be administered intracamerally.
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.
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 *cefuroxime*, 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 <1/10,000) 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 ≥1/10,
Common ≥1/100 to <1/10,
Uncommon ≥1/1000 to <1/100,
Rare ≥1/10,000 to <1/1000,
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 (*see Warnings and Precautions*).

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.

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

***In vitro* susceptibility of micro-organisms to Cefuroxime** Where clinical efficacy of cefuroxime has been demonstrated in clinical trials this is indicated with an asterisk (*).
Commonly Susceptible Species
Gram-Positive Aerobes: *Staphylococcus aureus* (methicillin susceptible)* *Coagulase negative staphylococcus* (methicillin susceptible) *Streptococcus pyogenes** Beta-hemolytic streptococci
Gram-Negative Aerobes: *Haemophilus influenzae* including ampicillin resistant strains* *Haemophilus parainfluenzae** *Moraxella catarrhalis** *Neisseria gonorrhoea** including penicillinase and non-penicillinase producing strains *Neisseria meningitidis* *Shigella* spp.
Gram-Positive Anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Spirochetes: Borrelia burgdorferi*
Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes: *Streptococcus pneumoniae** Viridans group streptococcus
Gram-Negative Aerobes: *Bordetella pertussis* *Citrobacter* spp. not including *C. freundii* *Enterobacter* spp. not including *E. aerogenes* and *E. cloacae* *Escherichia coli** *Klebsiella* spp. including *K. pneumoniae** *Proteus mirabilis* *Proteus* spp. not including *P. penneri* and *P. vulgaris* *Providencia* spp. *Salmonella* spp.
Gram-Positive Anaerobes: *Clostridium* spp.
Gram-Negative Anaerobes: *Bacteroides* spp. not including *B. fragilis* *Fusobacterium* spp.
Inherently resistant organisms
Gram-Positive Aerobes: *Enterococcus* spp. including *E. faecalis* and *E. faecium* *Listeria monocytogenes*
Gram-Negative Aerobes: *Acinetobacter* spp. *Burkholderia cepacia* *Campylobacter* spp. *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Morganella morganii* *Proteus penneri* *Proteus vulgaris* *Pseudomonas* spp. including *P. aeruginosa* *Serratia* spp. *Stenotrophomonas maltophilia*
Gram-Positive Anaerobes: *Clostridioides difficile*
Gram-Negative Anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* species *Mycoplasma* species *Legionella* species

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 probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level.

There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The major part is excreted in the first 6 hours.

Serum levels of cefuroxime are reduced by dialysis.

Non-Clinical Information

No additional data of relevance.

PHARMACEUTICAL INFORMATION

List of Excipients

None.

Each 750 mg vial contains 42 mg sodium (1.8 mEq).

Shelf-Life

The expiry date of the powder is indicated on the packaging.

The unopened pack storage temperature requirements are indicated on the packaging.

If unopened product previously stored below 25°C

Shelf life after reconstitution and dilution under controlled and validated aseptic conditions:

suspension and solution for Injection -5 hours below 25°C or 72 hours at 2 to 8°C

Solution for Infusion - 3 hours below 25°C or 72 hours at 2 to 8°C

Shelf life if reconstitution and dilution has not taken place in controlled and validated aseptic conditions:

The product should be used immediately or within 24 hours if stored at 2 to 8°C.

If unopened product previously stored below 30°C

Shelf life after reconstitution and dilution under controlled and validated aseptic conditions:

Suspension and solution for Injection - 5 hours below 25°C or 72 hours at 2 to 8°C

Solution for Infusion - Use immediately or within 24 hours at 2° to 8°C

Shelf life if reconstitution and dilution has not taken place in controlled and validated aseptic conditions:

The product should be used immediately or within 24 hours if stored at 2° to 8°C.

Storage

The storage conditions are detailed on the packaging.

Store in original package to 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.

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.

Use and 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 Information, 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).

1.5 g *ZINACEF* is compatible with azlocillin 1 g (in 15 ml) or 5 g (in 50 ml).

ZINACEF (5 mg/ml) is compatible with 5% w/v or 10% w/v xylitol injection.

ZINACEF may be constituted for i.m use with aqueous solutions containing up to 1% lidoocaine hydrochloride.

ZINACEF is compatible with the following more commonly used i.v. infusion fluids:

- 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 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.

Not all presentations are available in every country.

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IMPORTANT

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GSK Market is responsible to advise SDC when changes required impact the following:

Formulation
Tablet embossing
Storage conditions
Shelf Life

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