SUMMARY OF PRODUCT CHARACTERISTICS

ZINACEF™

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 solutuon for infusion (*MONOVIAL*)

CLINICAL PARTICULARS

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 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.

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 intravenous (i.v.) and/or intramuscular (i.m.) administration. *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 *Clostridium 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.

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 *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 ≥1/10,
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. not including *C. difficile*
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:
Clostridium 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.

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

Dry shelf life:

2 years at below 25°C.

Wet shelf life:

Suspensions of cefuroxime sodium for i.m. injection and aqueous solutions for direct i.v. injection retain their potency for 5 hours if kept below 25 °C and for 48 hours if refrigerated below 4 °C.

Special Precautions for Storage

Protect from light.

Some increase in the colour of prepared solutions and suspensions of *ZINACEF* may occur on storage.

Do not use ZINACEF after the expiry date shown on the vial label or carton.

Keep out the reach and sight of children.

Keep the vial in the outer carton to protect from light.

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% lidoocaine 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 mEqL) in 0.9% Sodium Chloride Injection.

Not all presentations are available in every country.

Manufactured by:
GlaxoSmithKline S.p.A. Manufacturing, Via A. Fleming, 2, Verona, 37135, Italy

Marketing Authorization Holder:
GlaxoSmithKline S.p.A., Via A. Fleming, 2, Verona, 37135, Italy

Date of issue: 07 July 2014