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Zinacef™

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Cefuroxime sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZINACEF Injection contains 250mg, 750mg, 1g and 1.5g of cefuroxime (as cefuroxime sodium).
ZINACEF MONOVIAL™ contains 750mg and 1.5g 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 i.v. and/or i.m. administration.
ZINACEF MONOVIAL is for iv infusion only.

GENERAL DOSING RECOMMENDATIONS

- **Adults**

Many infections respond to 750mg three times daily by i.m. or i.v. injection. For more severe infections the dose should be increased to 1.5g 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 6g. Where clinically indicated, some infections respond to 750mg or 1.5g 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 60mg/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**

1.5g 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:** – 3g 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 1.5g given i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations. This may be supplemented with two 750mg i.m. doses eight and sixteen hours later.
In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1.5g given i.v. with induction of anaesthesia, continuing with 750mg given i.m. three times daily for a further 24 to 48 hours.
In total joint replacement, 1.5g *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

1.5g *ZINACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500mg twice daily *ZINNAT* (cefuroxime axetil) oral therapy for 7 to10 days.

Acute exacerbations of chronic bronchitis

750mg *ZINACEF* three times daily or twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500mg 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 (750mg - 1.5g three times daily) until the creatinine clearance falls to 20ml/min or below.
In adults with marked impairment (creatinine clearance 10 - 20ml/min) 750mg twice daily is recommended and with severe impairment (creatinine clearance <10 ml/min) 750mg once daily is adequate.
For patients on haemodialysis a further 750mg 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 250mg 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 750mg 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 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 ≥1/10,
common ≥1/100 and <1/10,
uncommon ≥1/1000 and <1/100,
rare ≥1/10,000 and <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.

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

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 1ml Water for Injections to 250mg *ZINACEF* or 3ml Water for Injections to 750mg *ZINACEF*.
Shake gently to produce an opaque suspension.

Intravenous

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

Intravenous infusion

Dissolve 1.5g 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

1.5g *ZINACEF* constituted with 15ml Water for Injections may be added to metronidazole injection (500mg/100ml) and both retain their activity for up to 24 hours below 25°C.
1.5g *ZINACEF* is compatible with azlocillin 1g (in 15ml) or 5g (in 50ml) for up to 24 hours at 4°C or 6 hours below 25°C.
ZINACEF (5mg/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 40mEqL) in 0.9% Sodium Chloride Injection.

Not all presentations are available in every country.

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A., Verona, Italy

Version number: GDS28/IPI05
Date of issue: 04 January 2007

GlaxoSmithKline

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