Cefuroxime - Vit

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime - Vit

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials contain 750 mg cefuroxime (as sodium).

The total quantity of sodium per vial is 41.4 mg.

3. PHARMACEUTICAL FORM

Powder for solution or suspension for injection or infusion.
Cefuroxime is a white or almost white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefuroxime – Vit is indicated for the treatment of the infections caused by susceptible microorganisms, prophylaxis against post operative infections in a variety of operations.

4.2 Posology and method of administration

GENERAL DOSAGE RECOMMENDATIONS

Adults
Many infections will respond to 750 mg three times daily by IM or IV injection. For more severe infections, this dose should be increased to 1.5 g three times daily. IV. The frequency of IM or IV injections can be increased to six-hourly if necessary, giving total doses of 3 g to 6 g daily.

Infants and Children
Doses of 30 to 100 mg/kg/day given as three or four divided doses. A dose of 60 mg/kg/day will be appropriate for most infections.

Neonates
Doses of 30 to 100 mg/kg/day given as two or three divided doses. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults.

OTHER RECOMMENDATIONS

Gonorrhoea
1.5 g should be given as a single dose. This may be given as 2x750 mg injections (intramuscularly) into different sites, e.g. each buttock.

Meningitis
Cefuroxime is suitable for sole therapy of bacterial meningitis due to sensitive strains. The following doses are recommended:

Infants and Children
200 to 240 mg/kg/day IV in three or four divided doses. This dosage may be reduced to 100 mg/kg/day IV after three days or when clinical improvement occurs.

Neonates
The initial dosage should be 100 mg/kg/day IV. A reduction to 50 mg/kg/day IV may be made when clinically indicated.

Adults
3 g IV every eight hours. Data are not yet sufficient to recommend a dose for intrathecal administration.

Prophylaxis
The usual dose is 1.5 g IV with induction of anaesthesia for abdominal, pelvic and orthopedic operations, but may be supplemented with two 750 mg IM doses 8 and 16 hours later. In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1.5 g IV with induction of anaesthesia continuing with 750 mg IM three times daily for a further 24 to 48 hours.

In Total Joint Replacement
1.5 g cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

Table 1. *Recommended doses for Cefuroxime - Vit in renal impairment*

Creatinine clearance	T1/2 (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 affect the pharmacokinetics of cefuroxime.

4.3 Contraindications

Hypersensitivity to cefuroxime.

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.

Intracameral use and eye disorders

Cefuroxime - Vit is not formulated for intracameral use. Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intracameral use of cefuroxime sodium compounded from vials approved for intravenous/intramuscular administration. These reactions included macular oedema, retinal oedema, retinal detachment, retinal toxicity, visual impairment, visual acuity reduced, vision blurred, corneal opacity and corneal oedema.

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 or by *Bacteroides fragilis* (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

750 mg vial:
This medicinal product contains 41.4 mg sodium per vial, equivalent to 2.1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions 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: 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

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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). Cefuroxime - Vit 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 1/10; common 1/100 to < 1/10; uncommon 1/1,000 to < 1/100; rare 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
Infections and infestations			*Candida* overgrowth, overgrowth of *Clostridium difficile*
Blood and lymphatic system disorders	neutropenia, eosinophilia, decreased haemoglobin concentration	leukopenia, positive Coomb's test	thrombocytopenia, haemolytic anaemia
Immune system disorders			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
Gastrointestinal disorders		gastrointestinal disturbance	pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	transient rise in liver enzymes	transient rise in bilirubin	
Skin and subcutaneous tissue disorders		skin rash, urticaria and pruritus	erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome, angioneurotic oedema
Renal and urinary disorders			elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4)
General disorders and administration site conditions	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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

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)**	
	Susceptible	Resistant

Enterobacteriaceae[1]	≤8[2]	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	□0.5	>1
Streptococcus (other)	□0.5	>0.5
Haemophilus influenzae	□1	>2
Moraxella catarrhalis	□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 ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.

[4] The susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.

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

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
Gram-positive aerobes: *Staphylococcus aureus (methicillin-suscpetible)* $ *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae* *Streptococcus mitis* (viridans group)
Gram-negative aerobes: *Citrobacter* spp. not including *C. freundii* *Enterobacter* spp. not including *E. aerogenes* and *E. cloacae* *Escherichia coli* *Haemophilus influenzae* *Klebsiella pneumoniae*

Proteus mirabilis *Proteus* spp. not including *P. penneri and P. Vulgaris* *Providencia* spp. *Salmonella* spp.
Gram-positive anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Gram-negative anaerobes: *Fusobacterium* spp. *Bacteroides* spp.
Inherently resistant microorganisms
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium*
Gram-negative aerobes: *Acinetobacter* spp. *Burkholderia cepacia* *Campylobacter* spp. *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Morganella morganii* *Proteus penneri* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia marcescens* *Stenotrophomonas maltophilia*
Gram-positive anaerobes: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides fragilis*
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 Cmax 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 m^2 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 m^2 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. Clcr <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

None.

6.2 Incompatibilities

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions.

The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of Cefuroxime - Vit . However, if required, for patients receiving sodium bicarbonate injection by infusion the Cefuroxime - Vit may be introduced into the tube of the giving set.

Cefuroxime - Vit should not be mixed in the syringe with aminoglycoside antibiotics.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the vial in the outer carton in order to protect from light.

Shelf life after reconstitution:
Chemical and physical stability has been demonstrated for 8 hours at 25ºC and 48 hours at 2-8ºC.
Shelf life after dilution:
Chemical and physical stability has been demonstrated for 12 hours at 25ºC and 48 hours at 2-8ºC.

From a microbiological point of view the reconstituted solution should be used immediately. If reconstituted product is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C

unless the preparation has taken place under controlled and validated aseptic conditions.

6.5 Nature and contents of container

Glass (type III) vials with bromobutyl rubber stoper, flip-off cap.
Each pack contains 10 vials.

6.6 Special precautions for disposal and other handling

Instructions for constitution

Table 4. Additional volumes and concentrations which may be useful when fractional doses are required.

Additional volumes and concentrations, which may be useful when fractional doses are required				
Vial size	Routes of administration	Physical State	Amount of water to be added (mL)	Approximate cefuroxime concentration (mg/mL)* *
750 mg powder for solution for injection or infusion				
750 mg	intramuscular intravenous bolus intravenous infusion	suspension solution solution	3 mL 6 mL at least 25 mL*	216 116 116

* 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.*

Compatibility

Cefuroxime sodium is compatible with the following infusion fluids.
Dextrose 5% containing 20 mEq KCl
Heparin (10 and 50 units/ml) in 0.9% NaCl 10 and 40 mEq KCl in 0.9% NaCl
0.9% w/v Sodium Chloride Injection
5% Dextrose Injection
0.18% w/v Sodium Chloride plus 4% Dextrose Injection
5% Dextrose and 0.9% w/v 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
Lactated Ringer's Injection
M/6 Sodium Lactate Injection
Compound Sodium Lactate Injection BP (Hartmann's Solution).

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

7. MANUFACTURER:

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