1. NAME OF THE MEDICINAL PRODUCT

(SEFZITIL INJECTION) Cefuroxime for Injection USP 750mg and Sterile Water for Injection`

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Combi pack contains:

Each vial contains

Cefuroxime for injection USP 750mg	
Equivalent to Cefuroxime	750mg
Sterile Water for Injection USP	10ml

3. PHARMACEUTICAL FORM

Dry powder for injection; off white to slightly yellow powder

4. Clinical particulars

4.1 Therapeutic indications

Cefuroxime sodium for injection is indicated for the treatment of infections listed below in adults and children, including neonates (from birth):

- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis
- Complicated urinary tract infections, including pyelonephritis
- Soft-tissue infections: cellulitis, erysipelas and wound infections
- Intra-abdominal infections
- Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section)

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents.

Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults and children ≥ 40kg

Indication	Dosage
Community acquired pneumonia and acute exacerbations of chronic bronchitis	750 mg every 8 hours (Intravenously or intramuscularly)
Soft-tissue infections: cellulitis, erysipelas and	

wound infections.	
Intra-abdominal infections	
Complicated urinary tract infections, including pyelonephritis	1.5 g every 8 hours (Intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)	1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.
1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.	1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.

Children <40 kg

Community acquired pneumonia & Complicated Urinary Tract Infections (including pyelonephritis):

• Infants and toddlers > 3 weeks and children < 40 kg: 30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60mg/kg/day is appropriate for most infections

• Infants (birth to 3weeks): 30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.

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. Cephalosporin antibiotics may, in general, be given safely to patients who are hypersensitive to penicillins, although cross-reactions have been reported. Special care is indicated in patients who have experienced an anaphylactic reaction to penicillin.

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.

4.5 Interaction 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 probenicid is not recommended. Concurrent administration of probenecid prolongs the excretion of cefuroxime 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: Please refer to section 4.4.

Concomitant use with oral anticoagulants may give rise to increased international normalized ratio (INR).

4.6 Pregnancy and Lactation

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 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.

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 reported adverse drug reactions (ADRs) are diarrhoea, nausea, and vomiting. The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

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)

Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon

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

5.2 Pharmacodynamics properties

Pharmacotherapeutic Group: antibacterial 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.

The prevalence of 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 such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Gardnerella vaginalis

Staphylococcus aureus (methicillin-susceptible)

Streptococcus agalactiae

Streptococcus pneumoniae1

Streptococcus pyogenes and other beta-haemolytic streptococci

Streptococcus viridans group

Aerobic Gram-negative micro-organisms

Actinobacillus actinomycetemcomitans

Capnocytophaga spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms

Enterococcus faecium $

Aerobic Gram-negative micro-organisms

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris
Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Acinetobacter sp.
Citrobacter freundii
Enterobacter sp.
Legionella pneumophila
Morganella morganii

5.3 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 m2 following IM or IV administration over the dosage range of 250 to 1000 mg. Concentrations of cefuroxime more than 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 humor. 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 administration is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. Most of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m2 following IM or IV administration over the dosage range of 250 to 1000 mg.

5.4 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 None

6.2 Incompatibilities

Cefuroxime is compatible with most 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. However, if required, for patients receiving sodium bicarbonate injection by infusion the Cefuroxime solution may be introduced into the tube of the giving set.

Cefuroxime should not be mixed in the syringe with aminoglycoside antibiotics. In the absence of other compatibility studies, this medicinal product must not be mixed with other medicinal products apart from those listed as compatible in section 6.6.

6.3 Shelf life

Before reconstitution: 36 months.
In keeping with good pharmaceutical practice, freshly constituted suspensions or solutions should be used immediately. If this is not practicable then solution may be stored at 2°C-8°C (in a refrigerator) for up to 24 hours

6.4 Special precautions for storage

Store in a cool and dry place below 25°C, protect from light

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

Cefuroxime is supplied in Glass vial USP Type-III closed with bromo butyl rubber stopper, sealed with Al, Flip off Seal.

6.6 Special precautions for disposal <and other handling>

Instructions for constitution
Table 4. Additional volumes and solution/suspension concentrations which may be useful when fractional doses are required.

Additional volumes and solution/suspension concentrations, which may be useful when fractional doses are required				
Vial size	Routes of administration	Amount of water to be added (mL)	Approximate Cefuroxime concentration (mg/mL)**	Resulting product
750 mg	intramuscular intravenous bolus intravenous infusion	3 mL at least 6 mL at least 6 mL*	216 116 116	Suspension Solution Solution

* 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/suspension of cefuroxime in reconstitution medium is increased due to the displacement factor of the drug substance resulting in the listed concentrations in mg/ml.

As for all parenteral medicinal products, inspect the reconstituted solution or suspension visually for particulate matter and discoloration prior to administration.

Intramuscular injection: After addition of the specified amount of diluent for intramuscular injection, a suspension is formed.

Intravenous bolus injection or intravenous infusion: After addition of the specified amount of diluent for intravenous bolus or infusion, a clear solution is formed. The solution should only be used if the solution is clear and practically free from particles.

Solutions and suspensions range in colour from clear to yellow coloured depending on concentration, diluent and storage conditions used. When made up for intramuscular use, it becomes off-white and opaque. When made up for intravenous administration, it may be yellowish.

Compatibility

Cefuroxime sodium (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 24 hours at 25 °C.

Cefuroxime sodium is compatible with aqueous solutions containing up to 1% lidocaine hydrochloride.

Cefuroxime sodium is compatible with the following infusion fluids. It will retain potency for up to 24 hours at room temperature in:

0.9% Sodium Chloride Injection BP w/v

5% Dextrose Injection BP

0.18% w/v Sodium Chloride plus 4% Dextrose Injection BP

5% dextrose containing 0.9% Sodium Chloride Injection

5% dextrose containing 0.45% Sodium Chloride Injection

5% dextrose containing 0.225% Sodium Chloride Injection

10% Dextrose Injection

10% Invert Sugar in Water for Injection

7 APPLICANT

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