FRESENIUS KABI

CÓDIGO: ***Code***	798047	**DESIGNAÇÃO:** ***Name***	LIT.CEFUROXIME 0,75G INJ TRIMA	**ELABORADO POR:** ***Made by***	José Duarte
VERSÃO: ***Version***	/00	**PROVA:** ***Proof***	05	**DATA:** ***Date***	14 Ago.2013
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CORES: **Colours** ● Black ○ ○ ○ ○

Anexo 6.00 do PT.G.087

Cefuroxime – Fresenius 750mg

Powder for Solution for Injection

1 NAME OF THE MEDICINAL PRODUCT

Cefuroxime – Fresenius 750mg Powder for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 750 mg of cefuroxime (as 789 mg cefuroxime sodium).
Excipients:
Each vial contains 1.8 mmol (or 39 mg) of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
White to cream coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefuroxime 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.
In addition, it is an effective prophylactic against post-operative infection in a variety of operations.
Usually Cefuroxime sodium will be effective alone, but when appropriate it may be used in combination with an aminoglycoside antibiotic, or in conjuction with metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynaecological surgery.

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 and pharyngitis.
- Urinary tract infections for example, acute and chronic pyelonephritis, cystitis and symptomatic 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.

Cefuroxime is available as the axetil ester 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 cefuroxime sodium is effective when used prior to oral therapy with cefuroxime axetil in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

4.2 Posology and method of administration

Cefuroxime sodium injection for i.v. and/or i.m. administration

General Recommendations
Populations
Adults
Many infections respond to 750mg t.d.s by i.m. or i.v. injection. For more severe infections, this dose should be increased to 1500 mg t.d.s. i.v. The frequency of i.m. or i.v. injections can be increased to six hourly if necessary, giving total doses of 3g to 6g daily. Where clinically indicated, some infections respond to 750 mg or 1500 mg twice daily (i.v. or i.m.) followed by oral therapy with cefuroxime axetil.

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

Preterm (born at <36 weeks of gestation) and term newborn infants (age 0-27 days):
Cefuroxime is not recommended for the use in these age groups due to insufficient data on safety and efficacy. In the first weeks of life the serum half-life of cefuroxime can be three to five times than in adults (see section 5.2).

Gonorrhoea
Populations
Adults
1500 mg should be given as a single dose. This may be given as 2 x 750 mg i.m. injections into different sites, e.g. each buttock.

Meningitis
Cefuroxime sodium is suitable for sole therapy of bacterial meningitis due to sensitive strains.
Populations
Adults
3g given i.v. every 8 hours.

Infants and Children
150 to 250 mg/kg/day given i.v. in 3 or 4 divided doses.
(Note- Dosage of 200 to 240mg/kg/day i.v. in 3 or 4 divided doses has also been reported . This dosage may be reduced to 100mg/kg/day iv after three days or when clinical improvement occurs).

Prophylaxis
Populations
Adults
The usual dose is 1500 mg i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations. This may be supplemented with two 750mg i.m. doses 8 and 16 hours later.

In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1500 mg given i.v. with induction of anaesthesia, continuing with 750mg given i.m. t.d.s. for further 24 to 48 hours.
In total joint replacement, 1500 mg cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

Sequential Therapy
Populations
Adults
Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

Pneumonia: 1500 mg Cefuroxime sodium three times daily or twice daily for 48 to 72 h, followed by 500 mg twice daily cefuroxime axetil oral therapy for 7 to10 days.

Acute exacerbations of chronic bronchitis: 750 mg Cefuroxime sodium three times daily or twice daily for 48 to 72 h, followed by 500 mg twice daily cefuroxime axetil oral therapy for 5 to 10 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 Cefuroxime sodium should be reduced to compensate for its slower excretion.

Dosage in impaired renal function for adolescents, adults and elderly:
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min.

In patients with markedly impaired renal function the dosage of cefuroxime should be reduced as follows:

Creatinine clearance (ml/min)	Recommended dosage of cefuroxime (mg)	Frequency of dosage (hours)
> 20	normal dosage	
10-20	750	12
< 10	750	24
Patients on continous arteriovenous haemofiltration/haemodialysis	750	12

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision.
Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.

For patients on haemodialysis a further 750mg dose, by intravenous or intramuscular injection, should be given at the end of each session.
In addition to parenteral use, cefuroxime can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every two litres of dialysis fluid).

For low-flux haemofiltration follow the dosage recommended under impaired renal function.

Infants, toddlers (28 days to 23 months) and children (2 to 11 years) with impaired renal function:
There are insufficient data regarding use of cefuroxime in pediatric renal insufficiency and therefore such use is not recommended.

Route of Administration:
Cefuroxime may be administered by intramuscular injection, intravenous injection (within 3 - 5 minutes, see section 6.6). Intramuscular administration should be limited on special indication and/or exceptional clinical situations after benefit-risk-assessment. Intramuscular administration 3 times a day is not recommended.
Doses above 750 mg of cefuroxime should not be administered intramuscularly.

4.3 Contraindications

- Hypersensitivity to Cefuroxime, to any other cephalosporin antibiotics or to any of the components in this medication. .
- Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta lactamases.
If hypersensitivity reactions occur after administration of cefuroxime sodium, the use of Cefuroxime should be discontinued immediately and appropriate treatment measures should be initiated.

In patients who develop severe diarrhoea during or after use of cefuroxime sodium, the risk of life threatening pseudo-membranous colitis should be taken into account. The use of cefuroxime sodium should be discontinued and appropriate treatment measures should be established. The use of preparations inhibiting the intestinal peristaltic is contra-indicated.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide , aminoglycosides and amphotericin, as these combinations are suspected of adversely affecting renal function and increases the risk of nephrotoxicity. Renal function should be monitored in these patients, the elderly, and those with pre-existing renal impairment (see section 4.2).

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore the use in this patient group is not recommended.

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 cefuroxime sodium. Persistence of positive CSF cultures of *Haemophilus influenzae* at 18 to 36h has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

As with other antibiotics, use of cefuroxime 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 72h, then the parenteral course of treatment must be continued.
Please refer to the relevant prescribing information for cefuroxime axetil before initiating sequential therapy.

Special care should be taken in patients with hepatic dysfunction.

Cefuroxime solutions are incompatible with aminoglycoside antibiotics (see section 6.2).

Cefuroxime sodium use may result in a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (see section 4.8).

This medicine product contains 1.8 mmol (or 39 mg) of sodium per 750 mg dose which should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime sodium 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 Cefuroxime sodium.

This antibiotic does not interfere in the alkaline picrate assay for creatinine.

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol concomitantly with cefuroxime. Synergism may exist with aminoglycosides and metronidazole.

Concomitant therapy with probenecid can reduce the renal excretion of cephalosporins accompanied by higher and prolonged concentrations of cefuroxime in serum (see section 5.2).

4.6 Pregnancy and lactation

Use in pregnancy
There is no experimental evidence of embryopathic or teratogenic effects attributable to Cefuroxime but, as with all drugs it should only be used during pregnancy after careful risk/benefit assessment, especially during the first trimester.

Use during lactation
Cefuroxime is excreted in human milk. Cefuroxime should only be used during lactation after careful risk/benefit assessment. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 Effects on ability to drive and use machines

Cefuroxime has minor or moderate influence on the ability to drive and use machines. Cefuroxime may sometimes be associated with side effects, such as dizziness (see section 4.8).

4.8 Undesirable effects

The frequencies of undesirable effects are ranked according to the following:

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 (frequency cannot be estimated from the available data)
Dependent on the dose and duration of the treatment approximately 3 % of all treated patients are expected to experience one or several of the adverse reactions mentioned below.

Investigations
Not known: the use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.
Blood and lymphatic system disorders
Uncommon: eosinophilia, leucopenia, neutropenia, thrombocytopenia
Rare: decreased haemoglobin concentration, agranulocytosis
Very rare: haemolytic anemia.
Nervous system disorders
Uncommon: headache, dizziness
Very rare: vertigo, restlessness, nervousness, confusion
Gastrointestinal disorders
Common: gastrointestinal disturbances such as diarrhea, nausea and vomiting
Renal and urinary disorders
Common: increased levels of creatinine and urea in serum, especially in patients with impaired renal function (see section 4.2 and 4.4)

Uncommon: acute interstitial nephritis; Nephrotoxicity; Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment (see section 4.2 and 4.4)

Skin and subscutaneous tissue disorders

Common: skin rashes; urticaria; pruritus

Rare: erythema multiforme, *Stevens-Johnson* syndrome and toxic epidermal necrolysis

Infections and infestations

Rare: pseudomembranous colitis.

As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. *Candida*, *Enterococci* and *Clostridium difficile* (see section 4.4)

General disorders and administration site conditions

Common: pain at the injection site following intramuscular administration, thrombophlebitis and pain following intravenous injection, after rapid intravenous administration heat sensations or nausea may occur.

Rare: drug fever

Immune system disorders

Rare: Serum sickness

Very rare: Anaphylaxis (see section 4.4), cutaneous vasculitis

Not known: Angioneutrotic oedema

Hepatobiliary disorders

Uncommon: transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin

Very rare: jaundice

4.9 Overdose

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. There can be sequelae in form of brain damage. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties:

ATC classification

Pharmacotherapeutic group: Second-generation cephalosporines, ATC-Code: J01DC02

Mode of action:

The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins.

Mechanism of resistance:

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably depressed 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 M binding proteins in gram-negative organisms
- drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.

Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility.

Strains of Enterobacteriaceae, in particular *Klebsiella spp.* and *Escherichia coli* that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent *in vitro* susceptibility and should be considered as resistant.

Breakpoints:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints:

Organisms	Susceptible	Resistant
Enterobacteriaceae[1]	≤8 mg/l	> 8 mg/l
Staphylococcus spp	-*	-*
Streptococcus spp. (A, B, C, G)	≤0,5 mg/l	> 0,5 mg/l
Streptococcus pneumoniae	≤0,5 mg/l	> 1 mg/l
Haemophilus influenzae	≤ 1 mg/l	> 2 mg/l
Moraxella catarrhalis	≤ 1 mg/l	> 2 mg/l
Non-species related **	≤ 4 mg/1	> 8 mg/l

[1] The breakpoint pertains to a dosage of 1500 mg x 3 and to *E.coli* and *Klebsiella spp* only.

* Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility. Methicillin (Oxacillin)-resistant staphylococci are resistant to cephalosporines.

** Based on serum pharmacokinetic.

Susceptibility:

The prevalence of resistance may vary geographically and with time for selected species and local information 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
Gram positive aerobes
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus saprophyticus°
Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus mitis (viridans group)
Bordetella pertussis
Gram negative aerobes
Proteus mirabilis
Providencia spp.
Providencia rettgeri
Neisseria gonorrhoeae
Neisseria meningitidis
Salmonella spp.
Other organisms:
Borrelia burgdorferi
Species for which acquired resistance may be a problem
Gram positive aerobes
Staphylococcus epidermidis +
Staphylococcus haemolyticus+
Staphylococcus hominis+
Streptococcus pneumoniae+,3
Gram negative aerobes
Citrobacter freundii+
Citrobacter koseri+
Enterobacter aerogenes+
Enterobacter cloacae+
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumonia+
Moraxella catarrhalis
Inherently resistant organisms
Gram positive aerobes
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)[1,2]
Staphylococcus epidermidis (methicillin-resistant)
Gram negative aerobes
Acinetobacter baunsannii
Burkholderia cepacia
Campylobacter spp.
Morganella morganii
Proteus vulgaris
Pseudomonas aeruginosa
Serratia spp.
Stenotrophomonas maltophilia
Anaerobes
Bacteroides spp.
Clostridium diffrcile
Others
Chlamydia spp.
Chlamydophila spp.
Legionella spp.
Mycobacterium spp
Mycoplasma spp.
Acinetobacter calcoaceticus

° Refers to German data (March 2007): At the time of publication of the table no current data were available. In primary literature, standard text books, and treatment recommendations susceptibility is anticipated.

(+) Prevalence of bacterial resistance is >50% at least in one European country or region.

[1] Frequency of methicillin resistance is about 30 to 50% for all staphylococci in France and is usually observed in hospital.

[2] *Staphylococcus resistant* to methicillin are resistant to other beta-lactams.

[3] *Streptococcus resistant* to penicillin are always resistant to cefuroxime.

5.2 Pharmacokinetic properties

Absorption

Peak levels of cefuroxime are achieved within 30 to 45 min after i.m. administration.

Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Following intravenous doses of 750 mg and 1500 mg, serum peak concentrations (Cmax) were approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (tmax).

Distribution

Cefuroxime is widely distributed in the body and levels, that exceed the MIC-values of most pathogens, are achieved pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. The volume of distribution ranges between 9.3 and 15.8 l/1.73 m^2 in healthy adults. About 33% to 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Biotransformation

Cefuroxime is metabolized only to a minor extent (<5%).

Elimination

The elimination half-life ranges between about 70 and 80 min after intramuscular or intravenous administration in healthy adults. Most of the dose of cefuroxime is excreted unchanged in active form. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small amounts of cefuroxime are excreted in bile. The renal clearance is 136.0 and 169.6 ml/min/1.73 m^2 after 0.5 and 1 g cefuroxime intravenous and 137.9 and 146.3 ml/min/1.73 m^2 after 0.750 and I g cefuroxime intramuscular, respectively. The elimination is impaired in patients with impaired renal function.

Concomitant administration of oral probenecid slows tubular secretion of cefuroxime and decreases renal clearance by approximately 40%.

Oral probenecid (1 g) prolonged the half-life by 63% and increased the area under the concentration-time curve of intravenous cefuroxime (750 mg) by up to 50%.

Cefuroxime is dialysable and small amounts are removed by peritoneal dialysis.

Pharmacokinetics in special patient groups:

The half-life of cefuroxime is prolonged in patients with renal impairment associated with the risk of accumulation. The serum half-life is 4.2 hours at a creatinine clearance of 23 ml/min and 22.3 hours at a creatinine clearance of 5 ml/min. Therefore dose adjustment is required in patients with impaired renal function (see section 4.2).

The serum half-life is prolonged in preterm and term newborn infants during the first weeks of life (3 to 5 times the value in adults).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed in the syringe with aminoglycoside antibiotics.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

During intravenous administration cefuroxime should not be mixed with solutions containing other active substances.

6.3 Shelf life

24 months

Chemical and physical in-use stability has been demonstrated for 5 hours at 2°C to 8°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C

Keep the vials in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

15 ml type II colourless glass vials closed with siliconised rubber stoppers covered with aluminium caps and blue plastic flip off caps.

Pack sizes:

1 vial; 10 vials; 50 vials

Not all the pack sizes may be marketed

6.6 Special precautions for disposal

Compatibility with intravenous solutions

Chemical and physical in-use stability :Cefuroxime remains stable for 5 hours at 2°C to 8°C, if dissolved in:

- water for injections
- 0.9 % sodium chloride solution

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Instructions for reconstitution:

Cefuroxime 750 mg, powder for solution for injection, as intravenous injection:

Dissolve Cefuroxime 750 mg, powder for solution for injection, in 6 ml of water for injection or 0.9 % sodium chloride solution.

Cefuroxime 750 mg, powder for solution for injection, as intramuscular injection:

Dissolve Cefuroxime 750 mg, powder for solution for injection in 3 ml of water for injection or 0.9 % sodium chloride solution.

Shake gently to produce a clear solution.

The contents and concentrations of cefuroxime as solution are shown in the table below:

mg cefuroxime per vial	Intravenous Injection addition of ml solvent	Intramuscular Injection addition of ml solvent	Final volume ml	Concentration mg/ml
750	-	3	3.5	214
750	6	-	6.7	112

Note: Intravenous Cefuroxime injection should be given over 3 - 5 minutes.

The powder is white to cream coloured. The reconstituted solution is clear and colourless to yellowish. The reconstituted solution is for single use only and is to be inspected visually for particulate matter and discoloration prior to administration. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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01/2013

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it.

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