



Public Assessment Report

from the Norwegian Medicines Agency

Cefuroxim Farmaplus powder for solution or suspension for injection 250 mg
Cefuroxim Farmaplus powder for solution or suspension for injection 750 mg
Cefuroxim Farmaplus powder for solution for injection or infusion 1500 mg

Farmaplus AS, Norway
cefuroxime

MA-numbers in Norway: 02-1369(250 mg), 04-2521(750 mg), 04-2522(1500 mg)

Date: 2007-10-15

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure
Module 2: Summary of product Characteristics (SPC)
Module 3: Package Leaflet
Module 4: Labelling
Module 5: Scientific discussion
Module 6: Update

Module 1: Information about the initial procedure:

1. Type of application: Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity
2. Active substance: cefuroxime sodium
3. Pharmaceutical form: Powder for solution or suspension for injection and Powder for solution for injection or infusion
4. Strength: 250 mg, 750 mg and 1500 mg
5. MA holder: Farmaplus AS, Asker, Norway
6. Reference Member State: Norway
7. Concerned Member States: Denmark and Sweden
8. Procedure-number: : NO/H/0119/001-003/MR
9. Timetable:
Start (Day 0): 15.03.2007
End (Day 90): 13.06.2007

Module 2: Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxim FarmaPlus 250 mg, powder for solution or suspension for injection,
Cefuroxim FarmaPlus 750 mg, powder for solution or suspension for injection
Cefuroxim FarmaPlus 1500 mg, powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefuroxime sodium equivalent to cefuroxime 250 mg, 750 mg and 1500 mg

Sodium content:

250 mg: 13.8 mg (0.6 mmol)

750 mg: 41.4 mg (1.8 mmol)

1500 mg: 80.5 mg (3.5 mmol)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution or suspension for injection
Powder for solution for injection or infusion

White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The following serious infections caused by cefuroxime sensitive bacteria:

- Upper urinary tract infections
- Septicemia
- Acute bacterial meningitis
- Acute exacerbation of chronic bronchitis
- Pneumonia

The treatment should be re-evaluated when results from bacteriological examinations are available.

Pre-surgical prophylaxis in cases such as abdominal-, orthopaedic- and cardiac surgery when there is a risk of infections with Gram-negative bacteria.

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

4.2 Posology and method of administration

To be administered intramuscularly or intravenously as an injection within 3 – 6 minutes, or as an infusion within 20 – 30 minutes. Doses above 750 mg should not be administered intramuscularly.

Adults: 750 mg – 1500 mg every 8 hours depending on the nature and location of the infection.

Children: 30 – 100 mg/kg/24 hours divided in 3 doses, 60 mg/kg/24 hours is usually adequate for most infections.

Term newborn infants (0-27 days): 30 to 100 mg/kg/24 hours divided in 2 doses. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults.

Acute bacterial meningitis:

Children: 200 mg/kg/24 hours i.v. divided in 3 to 4 doses.

Term newborn infants (0-27 days): 100 mg/kg/24 hours divided in 2 doses.

Adults: 3 g i.v. every 8 hours.

Pre-surgical prophylaxis:

Adults and adolescents: 1.5 g i.v. 30-60 minutes prior to surgery.

Renal impairment in adult patients: For reduced kidney function the dose should be reduced according to the creatinine clearance. However, on the first day a single, normal dose (up to 1500 mg) should be administered.

Creatinine clearance (ml/min.)		Recommended daily dose
> 20		Normal dose
10 - 20		500-750 mg x 2
< 10		500-750 mg

For severe renal failure the serum concentration of cefuroxime should be monitored.

Patients undergoing haemodialysis will require a further 750 mg dose of cefuroxime at the end of each dialysis treatment. A suitable dosage for patients on continuous peritoneal dialysis is usually 750 mg twice daily.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

Monitoring of cefuroxime levels in serum: The concentrations of cefuroxime in serum should be monitored in patients with impaired renal function and when high doses of cefuroxime are given concomitantly with aminoglycosides or with potent diuretics.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any other cephalosporin antibiotics.

Cephalosporin allergy and type 1 reaction towards penicillins (anaphylactic, Quinckes edema and urticaria).

4.4 Special warnings and precautions for use

Special precautions must be exercised in patients that are allergic to penicillin or those with allergies of other beta-lactamies and a history of allergy. In renal failure the serum concentration should be monitored and the dose adjusted according to the creatinine clearance. Continued positive CSF cultures with *Haemophilus influenzae* have been reported after 18 – 36 hours.

High doses of cephalosporins should be given with caution to patients concomitantly treated with potent diuretics or aminoglycosides, since impaired renal function has been reported when these combinations are used. The concentrations of cefuroxime in serum and the renal function should be monitored in these patients (see section 4.2).

As with other broad spectrum antibiotics, prolonged use of cefuroxime sodium may result in overgrowth of non-susceptible organisms (e.g. *Candida*, enterococci, *Clostridium difficile*), which may require interruption of treatment.

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 the appropriate treatment established. Antiperistaltics are contra-indicated.

The sodium content of Cefuroxim FarmaPlus should be taken into account when prescribed to patients requiring sodium restriction.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraceptives (Birth control pills)

Antibiotics may in rare cases reduce the absorption and thereby the effect of the birth control pill.

Probenecide

Concomitant use of probenecide inhibits the tubular secretion and increases the plasma concentrations of cefuroxime.

Aminoglycosides

With concomitant use of cephalosporins and aminoglycosides it has been reported increased risk for oto- and nephro toxicity. Dose adjustment may be necessary.

4.6 Pregnancy and lactation

Pregnancy

Data from a limited number of epidemiological studies and experience with use in pregnant women indicate no adverse effects during pregnancy, on the foetus or in the new-born child. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/foetus via the placenta. Cefuroxim FarmaPlus should only be administered during pregnancy if the benefits outweigh the possible risk.

Lactation

Small amounts of the drug is excreted in breast milk. It is not likely that breastfed children will have any harmful effect from the drug, even though the risk of diarrhoea and fungus infections of the mucous membranes in the breast-fed infant cannot be excluded, 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 is not considered to have an influence on the ability to drive and use machines.

4.8 Undesirable effects

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.

Frequency	<i>Common</i> (>1/100 and < 1/10)	<i>Uncommon</i> (>1/1.000 and <1/100)	<i>Rare</i> (>1/10.000 and <1/1000)	<i>Very rare</i> (<1/10.000), including isolated reports
Organ group				

<i>Infections and infestations</i>			Pseudomembranous colitis (<i>e.g. Clostridium difficile</i>) see also section 4.4 <i>Superinfection (Candida)</i> in mouth-vagina-and intestinal mucosa	
Blood and lymphatic system disorders		Thrombocytopenia, eosinophilic disorder, neutropenia and leukopenia		Haemolytic anaemia
Immune system disorders	Hypersensitivity reactions, i.a. rashes, urticaria, pruritus,		Serum sickness	Anaphylaxis
Nervous system disorders		Headache, dizziness		Vertigo, restlessness, Nervousness, confusion
Ear and labyrinth disorders			Mild to moderate loss of hearing reported in some children treated for meningitis	
Gastrointestinal disorders	Gastrointestinal disturbances, diarrhoea, nausea and vomiting			
Hepato-biliary disorders		Transient rise in serum liver enzymes ALT (SGPT), AST (SGOT) and LDH		Jaundice
Skin and subcutaneous tissue disorders	Skin rashes, urticaria, Pruritus, see also immune system disorders		Erythema multiforme Stevens-Johnson syndrome, Toxic epidermal necrolysis (necrolysis exanthema)	
Renal and urinary disorders	Increased levels of creatinine and urea in serum, especially in patients with impaired renal function.	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		
General disorders and administration site conditions	Thrombophlebitis and pain following i.v. injection. After rapid i.v. administration heat sensations or nausea may occur.		Drug fever	

Investigations:

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.

4.9 Overdose

Overdose of cephalosporines may cause irritation in the brain tissue and result in convulsions. The plasma level of cefuroxime can be reduced with hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta lactam antibacterial agents.

ATC code: J01D C02

Mode of action

All cephalosporins (β -lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called Penicillin-Binding Proteins. After a β -lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.

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 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:

Cefuroxime – EUCAST (March 2006); Clinical MIC breakpoints (S \leq /R $>$):

<i>Enterobacteriaceae</i>	S \leq 8 mg/l, R $>$ 8 mg/l ⁽¹⁾ ,
<i>Staphylococcus</i>	Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility
<i>Streptococcus A,B,C,G</i>	S \leq 0.5 mg/l, R $>$ 0.5 mg/l
<i>S. pneumoniae</i>	S \leq 0.5 mg/l, R $>$ 1.0 mg/l
<i>H. influenzae</i>	
<i>M. catarrhalis:</i>	S \leq 1.0 mg/l, R $>$ 2.0 mg/l
Non-species related	

breakpoints: $S \leq 4.0 \text{ mg/l}$, $R > 8.0 \text{ mg/l}$

- (1) The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.

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. This has to be considered when interpreting the list below.

Commonly susceptible species
<u>Aerobes, Gram positive:</u> <i>Staphylococcus aureus</i> (MSSA) <i>Staphylococcus epidermidis</i> (MSSE) <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i>
<u>Aerobes, Gram negative:</u> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Proteus mirabilis</i> <i>Proteus rettgeri</i>
<u>Anaerobes:</u> <i>Peptococcus spp.</i> <i>Peptostreptococcus spp.</i>
Species for which resistance may be a problem: <i>Citrobacter spp.</i> <i>Enterobacter spp.</i> <i>Klebsiella spp.</i>
Inherently resistant organisms: <i>Acinobacter spp.</i> <i>Bacteroides fragilis</i> <i>Clostridium difficile</i> <i>Enterococcus spp.</i> <i>Listeria monocytogenes</i> <i>Morganella morganii</i> <i>Proteus vulgaris</i> <i>Pseudomonas spp.</i> <i>Serratia spp</i> <i>Streptococcus aureus</i> MRSE <i>Streptococcus epidermidis</i> MRSE <u>Others:</u> <i>Chlamydia spp.</i> <i>Chlamydophila spp.</i> <i>Mykobacterium spp.</i> <i>Mykoplasma spp.</i> <i>Rickettsia spp.</i> <i>Ureaplasma urealyticum</i>

5.2 Pharmacokinetic properties

Absorption

Cefuroxime is not absorbed from the gastrointestinal tract, and therefore parenteral administration is necessary.

Distribution

After intravenous administration of 750 mg cefuroxime, C_{max} is about 40-50 µg/ml. The C_{max} and the AUC (area under the concentration curve) increase with increasing dose.

The volume of distribution after intravenous administration of 750 mg is about 12.5 L.

The plasma-protein binding is 33-40%.

Cefuroxime levels, that exceed the MIC-values are achieved in bone tissue, synovial fluid and the aqueous humour.

Cefuroxime passes the blood-brain barrier in case of inflamed meninges.

Elimination

Cefuroxime is not metabolised, but is excreted unchanged through the kidneys via glomerular filtration and tubular secretion.

More than 90% of a dose of cefuroxime is excreted in the urine within 6 hours. Very high concentrations of active cefuroxime are found in the urine.

The half-life in adults is 1.1 to 1.5 hours.

Special populations

In new-borns, during the first weeks of life, the half-life can be 3 – 5 times longer than in adults. The elimination is impaired in patients with impaired renal function.

Haemodialysis increases the excretion of cefuroxime, necessitating increased dosage in patients undergoing haemodialysis, see 4.2.

5.3 Preclinical safety data

Cefuroxime sodium has a very low order of toxicity as shown in single and repeated dose toxicity studies. A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential

Studies in rabbit and mouse did not indicate any reproductive toxicity or teratogenic effects.

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

This medicinal product should not be mixed in the same syringe as amnioglycosides.

Should not be mixed with solutions with pH above 7,5, i.e. sodium hydrogen carbonate.

6.3 Shelf life

2 years.

Prepared solution/suspension

Intramuscular and intravenous injection: Chemical and physical stability has been demonstrated for 8 hours at 25°C and 24 hours at 2 – 8°C.

Intravenous infusion: Chemical and physical stability has been demonstrated for 12 hours at 25°C and 24 hours at 2 – 8°C.

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.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Glass vials with bromobutyl rubber stoppers in the following pack sizes:

250 mg: 10 vials

750 mg: 10 vials

1500 mg: 10 vials

Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility: Cefuroxim Farma Plus is compatible with the most commonly used solutions for infusion. Cefuroxim Farma Plus can be mixed with metronidazol, azlocillin and xylitol and is compatible with watercontaining solutions that contain up to 1% lidocaine chloride. Must not be mixed in the same syringe as amnioglycosides or diluted with sodium hydrogen carbonate for injection (see 6.2 Incompatibilities).

The vials fit the transfusion adapter for infusion in Mini-bags.

Intramuscular injection: Add at least 1 ml sterile water to 250 mg or 3 ml sterile water to 750 mg and mix gently for a suspension.

Intravenous injection: Add at least 2 ml sterile water to 250 mg or 6 ml sterile water to 750 mg or 15 ml sterile water to 1500 mg.

Intravenous infusion: Dissolve Cefuroxim FarmaPlus in at least 50 ml sodium chloride 9 mg/ml or glucose 50 mg/ml.

7. MARKETING AUTHORISATION HOLDER

FarmaPlus AS
P.O. Box 202
1372 ASKER
NORWAY

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

2007.06.13

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

CEFUROXIM FarmaPlus 250 mg, powder for solution or suspension for injection.
CEFUROXIM FarmaPlus 750 mg, powder for solution or suspension for injection.
CEFUROXIM FarmaPlus 1500 mg, powder for solution for injection or infusion.

Cefuroxime sodium

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. What Cefuroxim FarmaPlus is and what it is used for.
2. Before you use Cefuroxim FarmaPlus.
3. How to use Cefuroxim FarmaPlus.
4. Possible side effects.
5. How to store Cefuroxim FarmaPlus.
6. Further information

1. WHAT CEFUROXIM FARMAPLUS IS AND WHAT IT IS USED FOR

Cefuroxim FarmaPlus is an antibiotic, i.e. a drug effective against bacterial infections. It belongs to the group of antibiotics called cephalosporines.

Cefuroxim FarmaPlus is used for treatment of serious infections that are sensitive to the ingredient.

This is upper urinary tract infections, septicemia and acute bacterial meningitis, acute deterioration of chronic bronchitis and pneumonia.

Cefuroxim FarmaPlus is also used preventive for heart surgery, surgery of the stomach region and the muscle and skeleton system if there is a risk for infection of a certain type of bacteria (so-called Gram-negative bacteria).

2. BEFORE YOU USE CEFUROXIM FARMAPLUS

Do not use Cefuroxim FarmaPlus

The health care professional will not give you Cefuroxim FarmaPlus:

- if you are allergic (hypersensitive) to cefuroxime sodium or to any other cephalosporin antibiotics.
- if you have previously had strong allergic reactions to cephalosporines or penicillins (certain types of antibiotics).

Take special care with Cefuroxim FarmaPlus

The doctor will take special care:

- if you are allergic to penicillin
- if you have reduced kidney function

Using other medicines

Please tell your doctor or pharmacist if you are taking or recently have been taking any other medicines, including medicine obtained without a prescription.

The doctor will take special care if you are using any of the following medicinal products concomitantly:

- high doses of Cefuroxim FarmaPlus and medicinal products that may influence the kidneys (e.g. aminoglycoside antibiotics and certain strong diuretic drugs)
- Cefuroxim FarmaPlus and probenecid (medicinal product against gout)
- Cefuroxim FarmaPlus and birthcontrol pills, as the effect of the birthcontrol pills can be reduced.

Pregnancy and breast feeding

Experience in pregnant women is limited, but there are no indications of harmful effects. Cefuroxim FarmaPlus should however only be used if the advantage of using it outweighs the potential risk for the child.

The drug is only in limited degree excreted in breast milk. It is not likely that nursing infants will have harmful effects from the drug, even if the intestine- and the mouth flora may become affected.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Cefuroxim FarmaPlus does not influence the ability to drive or use machines.

Important information about some of the ingredients of Cefuroxim FarmaPlus

This medicinal product contains sodium, 250 mg cefuroxim contain 13.8 mg (0.6 mmol) sodium, 750 mg cefuroxim contain 41.4 mg (1.8 mmol) sodium and 1500 mg cefuroxim contain 80.5 mg (3.5 mmol) sodium. To be taken into consideration by patients on a controlled sodium diet

3. HOW TO USE CEFUROXIM FARMAPLUS

The doctor decides the dose which will be adjusted for your need. The medicinal product is given to you by a doctor or other health care professional. Cefuroxim FarmaPlus is delivered as dry powder that must be dissolved in sterile water or another suitable solution. The solution is injected into a blood vessel, into a muscle or it may be given as a drip infusion through a blood vessel.

If you take more Cefuroxim FarmaPlus than you should

Overdose of Cefuroxim FarmaPlus may cause onset of cramps. The treatment will be stopped immediately and cramp releasing treatment started.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cefuroxim FarmaPlus can cause side effects, although not everybody gets them.

Common (happens in more than 1 of 100 patients, but less than 1 of 10): Local irritation and phlebitis when injected intravenously and transient pain following intramuscular injection. Stomach and intestinal discomfort, diarrhoea, nausea and vomiting, hypersensitivity reactions i.e. skin reactions like itching, rash, urticaria, redness of the skin and excema. Increased level of creatinine and urea, especially in persons with impaired renal function.

Uncommon (happens in more than 1 of 1000 patients, but less than 1 of 100): Reduced amount of white blood cells, reduced amount of blood platelets, headache, dizziness, transient rise in certain liver enzymes, renal disorders (among other things kidney inflammation).

Rare (happens in more than 1 of 10.000 patients, but less than 1 of 1000): Serious allergic reactions, fever, serum sickness (allergic reaction that can give edema and joint pain), infection of the large

bowel, various serious skin disorders, mild to moderate hearing loss (reported in some children treated for meningitis), drug fever, yeast infections (Candida) in mouth-, vagina- and intestinal mucosa.

Contact a health care professional immediately if you have signs of serious allergic reactions, e.g. swelling of lips or face, breathing difficulties, serious skin reactions, severe and persistent diarrhoea, fever or are feeling ill.

Very rare (happens in less than 1 of 10.000): Serious allergic reactions, vertigo, nervousness, confusion, restlessness, anaemia, jaundice.

Cefuroxime may affect certain laboratory tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CEFUROXIM FARMAPLUS

Keep out of the reach and sight of children.

Do not store above 25°C.

Store in original package in order to protect from light.

Do not use Cefuroxim FarmaPlus after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cefuroxim FarmaPlus contains

- Active ingredient is cefuroxime sodium equal to cefuroxime 250 mg, 750 mg or 1500 mg.
- There are no excipients.

What Cefuroxim FarmaPlus looks like and contents of the pack

Pack sizes are 10x250 mg, 10x750 mg and 10x1500 mg

Marketing Authorization Holder:

FARMAPLUS AS
PO Box 202
1372 ASKER
NORWAY

Manufacturer:

FACTA SPA, Teramo, ITALY

For further information about this medicinal product, please contact the marketing authorization holder.

This leaflet was last approved in : 2007-06-13

The following information is intended for medical or healthcare professionals only:

Shelf-life after reconstitution:

Intramuscular and intravenous injection: Chemical and physical stability has been demonstrated for 8 hours

at 25°C and 24 hours at 2 – 8°C.

Intravenous infusion: Chemical and physical stability has been demonstrated for 12 hours at 25°C and 24

hours at 2 – 8°C.

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.

Compatibility:

Cefuroxim Farma Plus is compatible with the most commonly used solutions for infusion. Cefuroxim Farma Plus can be mixed with metronidazol, azlocillin and xylitol and is compatible with watercontaining solutions that contain up to 1% lidocaine chloride. Must not be mixed in the same syringe as amnioglycosides or diluted with sodium hydrogen carbonate for injection (see 6.2 Incompatibilities).

The vials fit the transfusion adapter for infusion in Mini-bags.

Intramuscular injection: Add at least 1 ml sterile water to 250 mg or 3 ml sterile water to 750 mg and mix gently for a suspension.

Intravenous injection: Add at least 2 ml sterile water to 250 mg or 6 ml sterile water to 750 mg or 15 ml sterile water to 1500 mg.

Intravenous infusion: Dissolve Cefuroxim FarmaPlus in at least 50 ml sodium chloride 9 mg/ml or glucose 50 mg/ml.

Module 4: Labelling

Not included

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Cefuroxim Farmaplus powder for solution or suspension for injection 250 mg and 750 mg and Cefuroxim powder for solution for injection of infusion 1500 mg. The procedure was finalised at 13.06.2007 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Cefuroxim Farmaplus powder for solution or suspension for injection 250 mg and 750 mg and Cefuroxim Farmaplus powder for solution for injection or infusion 1500 mg from Farmaplus AS. The first date of authorisation in Norway was 4. March 2004. The product is indicated for the following infections:

“The following serious infections caused by cefuroxime sensitive bacteria:

- Upper urinary tract infections
- Septicemia
- Acute bacterial meningitis
- Acute exacerbation of chronic bronchitis
- Pneumonia

The treatment should be re-evaluated when results from bacteriological examinations are available.

Pre-surgical prophylaxis in cases such as abdominal-, orthopaedic- and cardiac surgery when there is a risk of infections with Gram-negative bacteria.

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

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Zinacef «GlaxoSmithKline». Zinacef powder for solution or suspension for injection or infusion has been marketed in Norway since 02.11.1981. In addition, reference is also made to Zinacef authorisations in the individual Member States (reference product). This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. Since this product is a powder for solution or suspension and intended to be administered intravenously, a bioequivalence study is not necessary.

No new pre-clinical and clinical studies were conducted, which is acceptable for this generic application.

I. QUALITY ASPECTS

I.1 Introduction

Cefuroxim Farmaplus is presented in the form of a powder for solution or suspension for injection 250 mg and 750 mg and powder for solution for injection/infusion 1500 mg. The drug substance is added as cefuroxime sodium corresponding to 250 mg, 750mg and 1500 mg cefuroxime. No excipients have been used in the formulation. The powder for solution for injection/infusion is packed in vials made of colourless, transparent Ph. Eur. class III glass. The vials are closed with grey stoppers of bromobutyl rubber (type I) and a flip off cap..

I.2 2.2 Drug Substance

Cefuroxime sodium has a monograph in the Ph.Eur. and the manufacturer holds a Certificate of Suitability of the monograph. It is a white or almost white, slightly hygroscopic powder which is freely soluble in water.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are sufficiently described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

I.3 Medicinal Product

Cefuroxime powder for solution or suspension for injection 250 mg and 750 mg and powder for solution for injection/infusion 1500 mg is formulated without excipients. No raw materials of human or animal origin are used in the product. The product development has taken the physico-chemical characteristics of the active substance into consideration.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. The long term storage conditions are: Do not store above 25°C/60%RHC. Keep the vial in the outer carton in order to protect from light.

For in-use stability the chemical and physical in-use stability has been demonstrated for the prepared solution/suspension for intramuscular and intravenous injection 8 hours at room temperature (25 °C) and for intravenous infusion: 24 hours at 2 °C to 8 °C and for the solution for intravenous infusion 12 hours at 25 °C and 24 hours at 2 – 8 °C

II. NON-CLINICAL ASPECTS

Cefuroxim FarmaPlus has been shown to be essential similar to the approved product Zinacef “GlaxoSmithKline”. For this abridged application, non-clinical data have not been submitted and are not considered necessary.

III. CLINICAL ASPECTS

Cefuroxime is a well-known active substance with established efficacy and safety.

The generic product Cefuroxim “Farmaplus” is intended to be administered as an aqueous solution either intravenously or intramuscularly. It contains the same concentrations of the same active substance (cefuroxime sodium) as the currently authorised product in Norway (Zinacef “GlaxoSmithKline AS”). The test product (Cefuroxim “Farmaplus”) and the reference product

(Zinacef “GlaxoSmithKline AS”) do not contain excipients. For the above-mentioned reasons a bioequivalence study was not necessary and there was no need for evaluation of clinical efficacy and safety issues.

Cefuroxim ”Farmaplus”, powder for solution or suspension for injection 250 mg and 750 mg and powder for solution for injection/infusion 1500 mg, was given a Marketing Authorisation in 2004 in Norway with the following indications: “Serious infections like lower respiratory tract infections, upper urinary tract infections and sepsis, caused by cefuroxime sensitive micro-organisms. Initially in serious infections awaiting bacteriological determination. Bacterial meningitis.”

However, in May 2005 the Marketing Authorisation Holder applied for the following indication changes in section 4.1 “Therapeutic indications” in the SPC: “Acute bacterial meningitis, intra-abdominal infections, lower respiratory tract infections like acute exacerbations of chronic bronchitis and pneumonia, urogenital infections caused by gonococci, pre-surgical prophylaxis such as abdominal-, orthopaedic- and cardiac surgery when there is a risk of infections caused by Gram-negative species”.

The Applicant submitted 39 published articles to document the proposed indications. The use of cefuroxime in the treatment of various bacterial infections is well established and accordingly a bibliographical application is considered acceptable.

After an assessment of the submitted documentation it was concluded that the application contained an adequate review of published clinical data for the following sought indications: “Acute bacterial meningitis, intra-abdominal infections, acute exacerbation of chronic bronchitis, pneumonia, pre-surgical prophylaxis in cases such as abdominal-, orthopaedic- and cardiac surgery when there is a risk of infections with Gram-negative bacteria”.

During the discussions in the Mutual Recognition Procedure, the Reference Member State (Norway) and the Concerned Member States (Denmark and Sweden) finally agreed upon the indications that can be found in the approved SPC in Module 2 of this Public Assessment Report.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cefuroxim Farmaplus powder for solution or suspension for injection 250 mg and 750 mg and Cefuroxim Farmaplus powder for solution for injection or infusion 1500 mg is a generic to Zinacef «GlaxoSmithKline». Zinacef is a well-known medicinal product with an established efficacy and safety profile.

The product is an aqueous solution and intended to be administered intravenously. A bioequivalence study is therefore not necessary. The SPC is consistent with that of the original product.

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

The Member States mutually recognised the Norwegian evaluation and the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached through a written procedure.

Module 6: Update

List of abbreviations

CMD (h)	Co-ordination Group for Mutual Recognition and Decentralised procedures (human)
MA	Marketing Authorisation
SPC	Summary of Product Characteristics

