Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefuroxime 1500 mg powder for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 1500 mg of cefuroxime as 1578 mg of cefuroxime sodium.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime is indicated in the parenteral treatment of the following infections caused by sensitive pathogens
respiratory tract infections: e.g. acute and chronic bronchitis, bacterial pneumonia

- infections of the ear, nose and throat,
- urinary tract infections
- infections of skin and soft tissue
- bone and joint infections
- obstetric and gynaecological infections

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

4.2 Posology and method of administration

Route of Administration:
By intramuscular injection, intravenous injection or infusion.

Usual dosage for Adults and the Elderly:
Most infections will respond to cefuroxime 750 mg three times a day. For more severe infections, the dose may be increased to 1.5 g three times a day by intravenous injection.
The intramuscular method of administration is reserved to exceptional clinical situations and should undergo a risk-benefit assessment.
Special advice for intramuscular injection has to be regarded (see section 6.6, Special precautions for disposal of a used medicinal product or waste derived from such medicinal product and other handling of the product).

If necessary, the frequency of administration of cefuroxime can be increased to four times a day up to total daily doses of 3 g to 6 g.

Infants, toddlers and Children:
The daily dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most infections will respond to a dose of 60 mg/kg/day.

Neonates *(see section 5.2, Pharmacokinetic Properties).*
The daily dosage range is 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.

For impaired renal function:
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min. The recommended maintenance doses in impaired renal function are 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
CAPD patients	750	12
Patients on CAVH/CAVHD	750	12

Special precautions are required if creatinine clearance is <10 ml/minute under appropriate expert supervision.

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.

A dosage of 750 mg twice daily is recommended for patients in renal failure on continuous arteriovenous haemodialysis or high flux haemofiltration in intensive therapy units.

Cefuroxime is usually effective as a single therapy in the treatment of the above infections.

4.3 Contraindications

Hypersensitivity to Cefuroxime or to any other cephalosporin antibiotics.
Previous immediate and /or severe hypersensitivity reaction to penicillin or any beta-lactam drug.

4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to a penicillin or to any other type of beta-lactam drug.
If after administration of cefuroxime sodium sensitivity reactions occur, the use should be discontinued immediately and an appropriate treatment should be established.
Special care should be taken in patients with hepatic dysfunction.

As with other broad spectrum antibiotics, prolonged use of Cefuroxime sodium may result in the overgrowth of non-susceptible organisms (e.g., *candida*, *enterococci and clostridium dificile*, 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. The use of preparations inhibiting the intestinal peristaltic is contra-indicated (*See section 4.8, Undesirable effects*).

Long term use of cefuroxime sodium may lead to an excess of pathogens resistant to cefuroxime sodium. It is of high importance that the patient is carefully checked. If a super-infection occurs during treatment, appropriate measures should be taken (*See section 4.8, Undesirable effects*).

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving Cefuroxime sodium. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

Cefuroxime is excreted via the kidneys. Therefore a dosage adjustment is required in patients with impaired renal function (*see section 4.2, Posology and method of administration*).

4.5 Interaction with other medicinal products and other forms of interaction

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 concomitant use increases the risk of nephrotoxicity.

Concomitant therapy with probenecid can reduce the renal excretion of cephalosporins. Plasma concentrations are enhanced if probenecid is given concomitantly.

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.

Urine sugar tests using reduction methods may show false positive reactions, therefore enzymatic methods should be used (*see section 4.4, Special warnings and precautions for use*).

During intravenous administration admixture with other medications in solution should be avoided.

Sodium bicarbonate is not recommended for the dilution of Cefuroxime.
The use of cefuroxime sodium may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (See section 4.8, Undesirable effects).

4.6 Pregnancy and lactation

Use in pregnancy
There are not sufficient data on the use of cefuroxime sodium during pregnancy to assess its possible harmfulness. So far, animal tests have not yielded evidence of harmfulness. Cefuroxime crosses the placenta. Cefuroxime sodium should not be used during pregnancy unless considered essential by the physician.

Use during lactation
Cefuroxime is excreted to a small degree in human milk; breast feeding should be avoided in women using cefuroxime sodium.

4.7 Effects on ability to drive and use machines

Cefuroxime may sometimes be associated with side effects, such as dizziness, that may impair the ability to drive a vehicle, to operate machinery or to work safely (*See section 4.8, Undesirable effects*).

4.8 Undesirable effects

Common ((>1/100, <1/10)
Uncommon (>1/1,000,<1/100)
Rare (>1/10,000, <1/1,000)
Very rare (<1/10,000), including isolated reports.

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.

Blood and the lymphatic system disorders
In some patients decreased haemoglobin concentration, eosinophilia, leucopenia, neutropenia and thrombocytopenia might occur.
Very rare
Haemolytic anemia

Immune system disorders:
Rare
Serum sickness
Very rare
Anaphylaxis

Nervous system disorders
Uncommon
Headache, dizziness
Very rare
Vertigo, restlessness, nervousness, confusion

Ear and labyrinth disorders:
Mild to moderate hearing loss has been reported in some children treated for meningitis with cefuroxime.

Gastrointestinal disorders:
Common
Gastrointestinal disturbances such as diarrhoea, nausea and vomiting have been reported..

Hepato-biliary disorders:
Uncommon
Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin have been reported.
Very rare
Jaundice.

Skin and subcutaneous tissue disorders:
Common
Skin rashes, urticaria, pruritus.
Rare
Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Renal and urinary disorders
Common
Increased levels of creatinine and urea in serum have been reported commonly, especially in patients with impaired renal function.

Uncommon
Acute interstitial nephritis.
Nephrotoxicity has been reported. 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:
Rare
Drug fever

Common
Transient pain and induration may be commonly experienced at the site of intramuscular injection. This is more likely to occur with higher doses. Thrombophlebitis and pain may commonly follow intravenous injection. However, this is unlikely to be a cause for discontinuation of treatment. After rapid intravenous administration of cefuroxime heat sensations or nausea may occur. Dizziness and headache have been reported in patients who received cefuroxime.

Investigations
The use of cefuroxime may be accompanied by a false positive Coombstest. This may interfere with the performance of cross matching tests with blood.

4.9 Overdose

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. 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: cephalosporins and related substances
ATC-Code: J01D A06

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 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 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:
The following MIC breakpoints separating susceptible from intermediately susceptible organism and intermediately susceptible from resistant organisms are used.

Table 1: Susceptibility breakpoints.

Bacterial Breakpoints			**Organism**
NCCLS Breakpoints			
S:≤ 8 mg/L	I:16	R:≥32 mg/L	*Enterobacteriaceae*
S:≤ 4 mg/L	I:8	R:≥16 mg/L	*Enterococcus*
S:≤ 4 mg/L	I:8	R:≥16 mg/L	*Haemophilus influenzae*
S:≤ 1 mg/L	I:2	R:≥4 mg/L	*Neisseria gonorrhoeae*
S:≤ 0.5 mg/L	I:1	R:≥ 2 mg/L	*Streptococcus pneumoniae*
DIN Breakpoints			
S:≤ 4 mg/L	I:8	R:≥16 mg/L	All bacterial isolates
BSAC Breakpoints			
S:≤ 1 mg/L	I:2-16	R:≥32 mg/L	*Acinetobacter* spp. and
			Enterobacteriaceae
S:≤ 1 mg/L		R:≥ 2 mg/L	*Streptococcus pneumoniae, Moraxella*
			catarrhalis, Neisseria gonorrhoeae,
			Haemophilus influenzae

NCCLS: National Committee for Clinical Laboratory Standards,
DIN: Deutsches Institut für Normung,
BSAC:British Society for Antimicrobial Chemotherapy,
S: Susceptible, I: Intermediately susceptible, R: Resistant.

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
Aerobes, Gram positive: *Staphylococcus aureus* (methicillin-susceptible) Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*
Aerobes, Gram negative: *Escherichia coli* *Haemophilus influenzae* Klebsiella species *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Proteus mirabilis* *Proteus rettgeri*
Anaerobes, Peptococcus species Peptostreptococcus species
Other organisms: *Borrelia burgdorferi*.
Species for which resistance may be a problem
Acinetobacter species Citrobacter species Enterobacter species *Morganella morganii*
Resistant *Bacteroides fragilis* *Clostridium difficile* Enterococci *Listeria monocytogenes* *Proteus vulgaris* Pseudomonas species Serratia species

5.2 Pharmacokinetic properties

Absorption
Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Peak plasma concentration of 27 µg per ml have been achieved about 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose.

Distribution
Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Metabolism
Cefuroxime is not metabolized.

Elimination
Most of the dose of cefuroxime is excreted unchanged. 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.

Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life is about 70 minutes after either intramuscular, or intravenous injection and is prolonged in patients with renal impairment and in neonates.

5.3 Preclinical safety data

Cefuroxime sodium has a very low order of toxicity as demonstrated by acute toxicity studies. Investigations of chronic toxicity in several animal species (rat, dog and monkey) yielded no indications of drug related toxicological effects. The most prominent treatment-related effect was tissue damage at the injection sites.

A cefuroxime ester did not show clinically relevant effects when tested *in vitro* and *in vivo* for genotoxic potential Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.

No long-term investigations for determination of tumorigenic potential were performed.

Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogenic-effects. Cefuroxime has been shown to pass the placenta.

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 should not be mixed in the syringe with aminoglycoside antibiotics.

Mixing of cefuroxime with sodium bicarbonate solutions significantly affects the colour of the solution. Therefore, this solution is not recommended for the dilution of cefuroxime. If required, the cefuroxime solution in water for injections can be introduced into the tubing of the giving set in patients receiving sodium bicarbonate solution by infusion.

6.3 Shelf Life

3 years.

Reconstituted solution: Chemical and physical stability has been demonstrated for 2 hours at 25°C and for 24 hours at 2°C – 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 and would normally be no longer than 24h at 2 – 8 °C, unless reconstitution has taken place in controlled and validated aspetic conditions.

6.4 Special precautions for storage

Keep the containers in outer carton in order to protect from light..
Reconstituted solution: The product should be used immediately. Keep the vials in outer carton in order to protect from light.

6.5 Nature and contents of container

1500 mg powder for solution for injection:
15 ml vials of clear glass type III (Ph. Eur.) closed with rubber stopper and flip-off bordered caps.

Pack sizes: 1, 5, 10, 25, 50, 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Compatibility with intravenous solutions
Cefuroxime remains stable for 2 hours at room temperature and 24 h at 2 °C – 8 °C, if dissolved in:

- water for injections
- 0.9 % sodium chloride solution
- 5 % glucose solution

Instructions for reconstitution
Cefuroxime 250 and 750 mg, powder for solution / suspension for injection, as intramuscular administration: Add 1 ml of water for injections or 1.0 % lidocain, solution respectively to Cefuroxime 250 mg, powder for solution / suspension for injection and 3 ml to Cefuroxime 750 mg, powder for solution / suspension for injection. Shake gently to produce an homogenous suspension. Cefuroxime 1500 mg, powder for solution for injection, should not be administered intramuscularly.

Cefuroxime 250, 750 and 1500 mg, powder for solution / suspension for injection, as intravenous injection: Dissolve Cefuroxime 250 mg, powder for solution / suspension for injection g, in at least 2 ml of water for injections, 0.9 % sodium chloride solution or 5 % glucose solution Cefuroxime 750 mg, powder for solution / suspension for injection, in at least 6 ml and Cefuroxime 1500 mg, powder for solution for injection in 15 ml.

Shake gently to produce a clear solution.

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

mg cefuroxime per vial	addition of ml solvent	volume ml of final solution / suspension	Concentration mg/ml
250	2	2.2	114
750	6	6.8	110
1500	15	16.5	91
1500	50	51.5	29

Note: Antibiotics should not be added to routine infusion fluids. Most infusion fluids are given over 6 to 8 hours and this is impractical for antibiotic therapy. Cefuroxime should be given over short periods (30 minutes).
When reconstituted for intramuscular or intravenous injection, the white to almost white powder gives a colourless to slightly yellow suspension and a colourless to brownish-yellow solution respectively.

As for all parenteral medicinal products, inspect the reconstituted solution / suspension visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear. For single use only. Any remaining solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

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GU35 9QE
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8 MARKETING AUTHORISATION NUMBER

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