Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefuroxime Actavis 750 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefuroxime sodium equivalent to 750 mg cefuroxime.
Each 750 mg vial contains approximately 42 mg sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
Cefuroxime is white to faintly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime is indicated for the treatment of the following infections when caused by susceptible organisms.

Respiratory tract infections: acute exacerbation of chronic bronchitis, hospital acquired pneumonia, severe community acquired pneumonia.
Upper urinary tract infections: pyelonephritis.

Peri-operative prophylaxis against infection in abdominal, orthopaedic and cardiac surgery.

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

4.2 Posology and method of administration

Usual dosage for adolescents (aged 12 years to 17 years), adults and the elderly:
The dosage is 1.5 g/day to 6 g/day. In most infections a sufficient dose is 750 mg every 8 hours. In more severe infections the dose should be increased to 1.5 g every 8 hours by intravenous injection.
If necessary, the dosage frequency can be increased to every 6 hours up to total daily dose of 6 g.

Prophylaxis
The usual dose is 1.5 g intravenously with induction of anaesthesia for abdominal and orthopaedic operations, but may be supplemented with two 750 mg intramuscular doses eight and sixteen hours later. In cardiac operations, the usual dose is 1.5 g intravenously with induction of anaesthesia continuing with 750 mg intramuscularly three times daily for a further 24 hours to 48 hours.

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. The recommended maintenance dose in impaired renal function is as follows:

Creatinine clearance (ml/min)	Recommended dosage of cefuroxime (mg)	Frequency of dosage (hours)
>20	Normal dose	
10-20	750	12
<10	750	24
Patients on continuous arteriovenous haemofiltration/haemo-dialysis	750	12

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision (see section 4.4).

Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.

For patients on haemodialysis a further 750 mg dose, by intravenous or intramuscular injection, should be given at the end of each session.

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

Paediatric patients

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 that in adults (see section 5.2).

Infants, toddlers (age 28 days to 23 months) and children (2 years to 11 years):
The recommended 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.

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

Route of Administration:
Cefuroxime Actavis may be administered by intramuscular injection or 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 or to any of the cephalosporins.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta−lactam medicinal products.

4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If after administration of cefuroxime sodium hypersensitivity reactions occur, the use of cefuroxime sodium should be discontinued immediately and an appropriate treatment measures should be initiated.

Special care should be taken in patients with hepatic dysfunction.

As with other antibiotics, use of cefuroxime sodium 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.

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. Anti-peristaltics are contra-indicated.

Cefuroxime solution is incompatible with aminoglycoside antibiotics (see section 6.2).

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 (see section 4.8).

Cefuroxime is excreted via the kidneys. Therefore a dose adjustment is required in patients with impaired renal function (see section 4.2).

Due to an increased risk of cefuroxime accumulation in serum accompanied by an increased risk for undesirable effects patients with a creatinine clearance < 10 ml/min should be treated under expert supervision.

As a precaution, renal function should be monitored if renal function is already impaired.

The sodium content of cefuroxime 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.

This medicinal product contains 1.8 mmol (42 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

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, amphotericin and aminoglycosides, as concomitant use increases the risk of nephrotoxicity.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins. Therefore, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.

Probenicid inhibits the tubular excretion of cefuroxime. When probenicid is administered concomitantly plasma concentrations of cefuroxime are enhanced.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of cefuroxime on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience Cefuroxime Actavis should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation
Cefuroxime is excreted in human milk. Cefuroxime Actavis 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 may sometimes be associated with side effects, such as dizziness, that may impair the ability to drive a vehicle, operate machinery or to work safely.

4.8 Undesirable effects

The following convention has been used for the classification of frequency:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000, not known (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.

System Organ Class	Frequency	Undesirable effects
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).
Blood and lymphatic system disorder	Uncommon	Eosinophilia, leucopenia, neutropenia, thrombocytopenia
	Rare	Decreased haemoglobin concentration, agranulocytosis
	Very rare	Haemolytic anemia
Immune system disorders	Rare	Serum sickness
	Very rare	Anaphylaxis (see section 4.4)
	Not known	Angioneutrotic oedema
Nervous system disorders	Uncommon	Headache, dizziness
	Very rare	Vertigo, restlessness, nervousness, confusion
Gastrointestinal disorders	Common	Gastrointestinal disturbances such as diarrhoea, nausea and vomiting
Hepatobiliary disorders	Uncommon	Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin
	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, 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).
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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

Pharmacotherapeutic group: Second generation cephalosporin
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, resulting in bacterial lysis.

PK/PD relationship
The efficacy is mainly determined by the length of time, during which the drug level is above the minimal inhibitory concentration of the pathogen.

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
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/l	> 8 mg/l

[1] The breakpoint pertains to a dosage of 1.5 g 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.

Susceptability
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is 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
Gram negative aerobes
Proteus mirabilis
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 pneumoniae[+]
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 baumannii
Burkholderia cepacia
Campylobacter spp.
Morganella morganii
Proteus vulgaris
Pseudomonas aeruginosa
Serratia spp.
Stenotrophomonas maltophilia
Anaerobes
Bacteroides spp.
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Legionella spp.
Mycobacterium spp.
Mycoplasma spp.

° 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
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 1.5 g, serum peak concentrations (C_{max}) were

approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (t_{max}).
Peak plasma concentrations 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 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 1 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.

Linearity/non-linearity
The peak plasma concentration and the area under the concentration curve increase with increasing dose.

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).

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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.
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. No long-term investigations for the determination of a 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

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

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 powder for solution for injection. However, if required, for patients receiving sodium bicarbonate injection by infusion the cefuroxime powder for solution for injection may be introduced into the tube of the giving set.

Cefuroxime powder for solution for injection should not be mixed in the syringe with aminoglycoside antibiotics.

6.3 Shelf life

2 years.

Reconstituted product:
Chemical and physical in-use stability has been demonstrated for 24 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 prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

20 ml type I glass vials, sealed with grey bromo butyl rubber stopper and coloured flip off seal.

Pack sizes:
1 vial, 5 vials, 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Preparation of solution
Intramuscular
3 ml water for injections to 750 mg Cefuroxime Actavis. Shake gently to produce an opaque suspension.

Intravenous
Dissolve Cefuroxime Actavis in water for injections using 6 ml for 750 mg. The reconstituted solution should appear yellowish.

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

Cefuroxime per vial (mg)	Route of administration	Volume of solvent to be added (ml)	Final volume of solution (ml)	Concentration of solution (mg/ml)
250	IM	1	1.2	208
	IV Bolus	2	2.2	114
750	IM	3	3.5	214
	IV Bolus	6	6.7	112
1500	IV Bolus	15	16.2	93
	IV Infusion	50	51.2	29

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions. Water for injections is recommended for reconstitution, followed by dilution (prior to intravenous administration) with water for injections, 5% glucose injection or 0.9% sodium chloride injection.
Cefuroxime sodium is also compatible with Hartmann's solution and 0.18% sodium chloride + 4% glucose.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/66/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th November 2010

10 DATE OF REVISION OF THE TEXT

August 2016