

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

CEFUROXIME ACTAVIS (750 mg, 1.5 g, powder for injection/infusion)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFUROXIME ACTAVIS vials contain 750 mg, or 1.5 g of cefuroxime (as cefuroxime sodium) powder for injection or infusion.

## 3. PHARMACEUTICAL FORM

Powder for injection/ infusion.

Cefuroxime is a white to or almost white powder which produces an off-white suspension for intramuscular use or a yellow solution of intravenous administration after reconstitution with water. Variations in the intensity of this colour do not indicate any change in either the efficacy or safety of the product.

## 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. Susceptibility to cefuroxime sodium will vary with geography and time and local susceptibility data should be consulted where available (see **Pharmaceutical particulars** and **Pharmacodynamic Properties**).

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, pharyngitis and otitis media.
- Urinary tract infections for example, acute and chronic pyelonephritis, cystitis and asymptomatic 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.

Usually CEFUROXIME ACTAVIS will be effective alone, but when appropriate it may be used in combination with an aminoglycoside antibiotic, or in conjunction with metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynaecological surgery (see **Pharmaceutical particulars**).

Where appropriate CEFUROXIME ACTAVIS is effective when used prior to oral therapy with cefuroxime axetil in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

## **4.2 Dose and method of administration**

CEFUROXIME ACTAVIS Injection for intravenous (IV) and/or intramuscular (IM) administration.

No more than 750 mg should be injected at one intramuscular site.

For instructions on reconstitution/dilution of the product before administration, see **Special precautions for disposal and other handling**.

### **General Recommendations**

#### Adults

Many infections respond to 750mg three times daily by intramuscular or intravenous injection. For more severe infections the dose should be increased to 1.5g three times daily given intravenously. The frequency of administration may be increased to 6-hourly if necessary, giving total daily doses of 3 to 6g. Where clinically indicated, some infections respond to 750mg or 1.5g twice daily (intravenously or intramuscularly) followed by oral therapy with cefuroxime axetil.

#### Infants and Children

30 to 100mg/kg/day given as 3 or 4 divided doses. A dose of 60mg/kg/day is appropriate for most infections.

#### Neonates

30 to 100mg/kg/day given as 2 or 3 divided doses. (see Pharmacokinetic Properties).

### **Gonorrhoea**

#### Adults

1.5g as a single dose (as 2 x 750mg injections given intramuscularly with different sites, e.g. each buttock).

### **Meningitis**

CEFUROXIME ACTAVIS is suitable for sole therapy of bacterial meningitis due to sensitive strains.

#### Adults

3g given intravenously every eight hours.

#### Infants and Children

150 to 250mg/kg/day given intravenously in 3 or 4 divided doses.

#### Neonates

The dosage should be 100mg/kg/day given intravenously.

### **Prophylaxis**

#### Adults

The usual dose is 1.5g given intravenously with induction of anaesthesia for abdominal, pelvic and orthopaedic operations. This may be supplemented with two 750mg intramuscular doses eight and sixteen hours later.

In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1.5g given intravenously with induction of anaesthesia, continuing with 750mg given intramuscularly three times daily for a further 24 to 48 hours.

In total joint replacement, 1.5g cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

## **Sequential therapy**

### Adults

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

Pneumonia: 1.5g CEFUROXIME ACTAVIS three times daily or twice daily (given intravenously or intramuscularly) for 48 to 72 hours, followed by 500mg twice daily cefuroxime axetil oral therapy for 7 to 10 days.<sup>4</sup>

Acute exacerbations of chronic bronchitis: 750mg CEFUROXIME ACTAVIS three times daily or twice daily (given intravenously or intramuscularly) for 48 to 72 hours, followed by 500mg twice daily cefuroxime axetil oral therapy for 5 to 10 days.

## **Impaired Renal Function**

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 ACTAVIS should be reduced to compensate for its slower excretion.

It is not necessary to reduce the standard dose (750mg to 1.5g three times daily) until the creatinine clearance falls to 20mL/min or below.

In adults with marked impairment (creatinine clearance 10 to 20mL/min) 750mg twice daily is recommended and with severe impairment (creatinine clearance <10 mL/min) 750mg once daily is adequate.

For patients on haemodialysis a further 750mg dose should be given intravenously or intramuscularly at the end of each dialysis. In addition to parenteral use, cefuroxime can be incorporated into the peritoneal dialysis fluid (usually 250mg for every 2 litres of dialysis fluid).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units a suitable dosage is 750mg twice daily. For low-flux haemofiltration follow the dosage recommended under impaired renal function.

Cefuroxime is also available as the axetil ester for oral administration. This permits parenteral therapy with cefuroxime to be followed by oral therapy in situations where a change from parenteral to oral is clinically indicated.

## **4.3 Contraindications**

Hypersensitivity to cephalosporin antibiotics.

## **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-lactams.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides, as renal impairment has been reported with these combinations. Renal function should be monitored in these patients, the elderly, and those with pre-existing renal impairment (see Dosage and Administration).

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 cerebral spinal fluid (CSF) cultures of *Haemophilus influenzae* at 18 to 36 hours 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.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

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 72 hours, then the parenteral course of treatment must be continued.

Refer to the relevant prescribing information for cefuroxime axetil before initiating sequential therapy.

#### **4.5 Interaction with other medicines and other forms of interaction**

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

CEFUROXIME ACTAVIS 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 ACTAVIS.

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

#### **4.6 Fertility, pregnancy and lactation**

There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime, but, as with all medicines, it should be administered with caution during the early months of pregnancy.

Cefuroxime is excreted in human milk, and consequently caution should be exercised when CEFUROXIME ACTAVIS is administered to a nursing mother.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/1000)

were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

Very common  $\geq 1/10$ ,  
Common  $\geq 1/100$  to  $< 1/10$ ,  
Uncommon  $\geq 1/1000$  to  $< 1/100$ ,  
Rare  $\geq 1/10,000$  to  $< 1/1000$ ,  
Very rare  $< 1/10,000$ .

### **Infections and infestations**

Rare Candida overgrowth.

### **Blood and lymphatic system disorders**

Common Neutropenia, eosinophilia.

Uncommon Leukopenia, decreased haemoglobin concentration, positive Coomb's test.

Rare Thrombocytopenia.

Very rare Haemolytic anaemia.

Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coomb's Test (which can interfere with cross matching of blood) and very rarely haemolytic anaemia.

### **Immune system disorders**

Hypersensitivity reactions including

Uncommon Skin rash, urticaria and pruritus.

Rare Drug fever.

Very rare Interstitial nephritis, anaphylaxis, cutaneous vasculitis.

See also Skin and subcutaneous tissue disorders and Renal and urinary disorders.

### **Vascular disorders**

Common Thrombophlebitis may follow intravenous injection.

### **Gastrointestinal disorders**

Uncommon Gastrointestinal disturbance.

Very rare Pseudomembranous colitis (see Warnings and Precautions).

### **Hepatobiliary disorders**

Common Transient rise in liver enzymes.

Uncommon Transient rise in bilirubin.

Transient rises in serum liver enzymes or bilirubin occur, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver.

### **Skin and subcutaneous tissue disorders**

Very rare Erythema multiforme, toxic epidermal necrolysis and Stevens Johnson Syndrome.

See also Immune system disorders.

### **Renal and urinary disorders**

Very rare Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (See **Special warnings and precautions for use**).

See also Immune system disorders.

### **General disorders and administration site conditions**

Common Injection site reactions which may include pain and thrombophlebitis

Pain at the intramuscular injection site is more likely at higher doses. However it is unlikely to be a cause for discontinuation of treatment.

### **Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

### **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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antibacterials for systemic use (Second generation cephalosporin), ATC Code: J01DC02

### **Mechanism of Action**

Cefuroxime is a well characterised and effective antibacterial agent which has bactericidal activity against a wide range of common pathogens, including  $\beta$ -lactamase producing strains.

Cefuroxime has good stability to bacterial  $\beta$ -lactamase, and consequently is active against many ampicillin-resistant or amoxicillin-resistant strains.

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

### **Pharmacodynamic Effects**

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

### **In vitro susceptibility to micro-organisms to Cefuroxime**

Where clinical efficacy of cefuroxime has been demonstrated in clinical trials this is indicated with an asterisk (\*)

### *Commonly Susceptible Species*

#### **Gram-Positive Aerobes:**

Streptococcus aureus (methicillin susceptible)\*  
Coagulase negative staphylococcus (methicillin susceptible)  
Streptococcus pyogenes\*  
Beta-hemolytic streptococci

#### **Gram-Negative Aerobes:**

Haemophilus influenzae including ampicillin resistant strains\*  
Haemophilus parainfluenzae\*  
Moraxella catarrhalis\*  
Neisseria gonorrhoea\* including penicillinase and non-penicillinase producing strains  
Neisseria meningitidis  
Shigella spp.

#### **Gram-Positive Anaerobes:**

Peptostreptococcus spp.  
Propionibacterium spp.

#### **Spirochetes:**

Borrelia burgdorferi\*

### *Organisms for which acquired resistance may be a problem*

#### **Gram-Positive Aerobes:**

Streptococcus pneumoniae\*  
Viridans group streptococcus

#### **Gram-Negative Aerobes:**

Bordetella pertussis  
Citrobacter spp. not including C. freundii  
Enterobacter spp. not including E. aerogenes and E. cloacae  
Escherichia coli\*  
Klebsiella spp. including K. pneumoniae\*  
Proteus mirabilis  
Proteus spp. not including P. penneri and P. vulgaris  
Providencia spp.  
Salmonella spp.

#### **Gram-Positive Anaerobes:**

Clostridium spp. not including C. difficile

#### **Gram-Negative Anaerobes:**

Bacteroides spp. not including B. fragilis  
Fusobacterium spp.

### *Inherently resistant organisms*

#### **Gram-Positive Aerobes:**

Enterococcus spp. including E. faecalis and E. faecium

Listeria monocytogenes
<p><b><u>Gram-Negative Aerobes:</u></b>  Acinetobacter spp.  Burkholderia cepacia  Campylobacter spp.  Citrobacter freundii  Enterobacter aerogenes  Enterobacter cloacae  Morganella morganii  Proteus penneri  Proteus vulgaris  Pseudomonas spp. including P. aeruginosa  Serratia spp.  Stenotrophomonas maltophilia</p>
<p><b><u>Gram-Positive Anaerobes:</u></b>  Clostridium difficile</p>
<p><b><u>Gram-Negative Anaerobes:</u></b>  Bacteroides fragilis</p>
<p><b><u>Others:</u></b>  Chlamydia species  Mycoplasma species  Legionella species</p>

## 5.2 Pharmacokinetic properties

### Absorption

Peak levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration.

### Distribution

Protein binding has been variously stated as 33 to 50% depending on the methodology used.

Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

### Metabolism

Cefuroxime is not metabolised and is excreted by glomerular filtration and tubular secretion.

### Elimination

The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes.

In the first weeks of life the serum half-life of cefuroxime can be 3 to 5 times that in the adult.

Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level. There is an almost complete recovery (85-90%) of unchanged cefuroxime in urine within 24 hours of administration. The major part is excreted in the first six hours. Serum levels of cefuroxime are reduced by dialysis.



### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins; however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

None.

### **6.2 Incompatibilities**

CEFUROXIME ACTAVIS should not be mixed in the syringe with aminoglycoside antibiotics.

CEFUROXIME ACTAVIS should not be mixed with solutions with pH above 7.5 ie. sodium hydrogen carbonate. For patients receiving Sodium Bicarbonate Injection by infusion the CEFUROXIME ACTAVIS may be introduced into the tube of the giving set.

### **6.3 Shelf life**

#### Dry powder:

24 months at 25 °C.

#### Reconstituted suspension:

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

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

Protect from light.

Some increase in the colour of prepared solutions and suspensions of CEFUROXIME ACTAVIS may occur on storage.

### **6.5 Nature and contents of container**

Each pack contains 10 vials.

### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal. Any unused medicine or waste material should be disposed of in accordance with local requirements.

### **Instructions for use/handling**

#### *Intramuscular*

Add 3mL Water for Injections to 750mg CEFUROXIME ACTAVIS. Shake gently to produce an opaque suspension.

### ***Intravenous***

Dissolve CEFUROXIME ACTAVIS in Water for Injections using at least 6mL for 750mg, or at least 15mL for 1.5g.

### ***Intravenous infusion***

Dissolve 1.5g of cefuroxime sodium in 15 ml of Water for Injections. Add the reconstituted solution of cefuroxime sodium to 50 or 100 ml of a compatible infusion fluid (see information on Compatibility below). These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids.

### ***Compatibility***

1.5g CEFUROXIME ACTAVIS constituted with 15mL Water for Injections may be added to metronidazole injection (500mg/100mL) and both retain their activity for up to 24 hours below 25°C.

1.5g CEFUROXIME ACTAVIS is compatible with azlocillin 1g (in 15mL) or 5g (in 50mL) for up to 24 hours at 4°C or 6 hours below 25°C.

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

CEFUROXIME ACTAVIS is compatible with aqueous solutions containing up to 1% lignocaine hydrochloride.

CEFUROXIME ACTAVIS is compatible with the more commonly used intravenous infusion fluids. It will retain potency for up to 24 hours at room temperature in:

Sodium Chloride Injection BP 0.9% w/v.

5% Dextrose Injection BP.

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

5% Dextrose and 0.9% Sodium Chloride Injection.

5% Dextrose and 0.45% Sodium Chloride Injection.

5% Dextrose and 0.225% Sodium Chloride Injection.

10% Dextrose Injection.

10% Invert Sugar in Water for Injection.

Ringer's Injection USP.

Lactated Ringer's Injection USP.

M/6 Sodium Lactate Injection.

Compound Sodium Lactate Injection BP (Hartmann's Solution).

The stability of CEFUROXIME ACTAVIS in Sodium Chloride Injection BP 0.9% w/v and in 5% Dextrose Injection is not affected by the presence of hydrocortisone sodium phosphate.

CEFUROXIME ACTAVIS has also been found compatible for 24 hours at room temperature when admixed in intravenous infusion with:

Heparin (10 and 50 units/mL) in 0.9% Sodium Chloride Injection; Potassium Chloride (10 and 40mEqL) in 0.9% Sodium Chloride Injection.

## **7. MEDICINE SCHEDULE**

Prescription Medicine

## 8. SPONSOR

Teva Pharma (New Zealand) Limited  
PO Box 128244  
Remuera  
Auckland 1541  
Telephone: 0800 800 097

## 9. DATE OF FIRST APPROVAL

20<sup>th</sup> November 2014

## 10. DATE OF REVISION OF THE TEXT

05<sup>th</sup> July 2017

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Complete Data Sheet	-Updated to SPC style format as per Medsafe's data sheet consultation.
8. Sponsor	-Sponsor name changed from Actavis New Zealand Limited to Teva Pharma (New Zealand) Ltd -Sponsor address changed from street address to P.O box address -Telephone number changed to 0 800 800 097
4.2 Dose and method of administration	Updates made in line with innovator's latest data sheet on Medsafe's website (Zinacef, Date of preparation: 6 <sup>th</sup> Feb 2017).
5.1 Pharmacodynamic properties	Updates made in line with innovator's latest data sheet on Medsafe's website (Zinacef, Date of preparation: 6 <sup>th</sup> Feb 2017).
5.3 Preclinical safety data	Information provided in this section based on innovator's current EU SPC (Zinacef, Date of revision: 31 <sup>st</sup> July 2015).