Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Restum 250/500 Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains: Cefuroxime Axetil USP
Equivalent to Cefuroxime .....250/500 mg

Excipients of known activity
None

3. Pharmaceutical form

Film Coated Tablets
White coloured, elongated, biconvex, film coated tablets having both side plain.

4. Clinical particulars

4.1 Therapeutic indications

Acute Otitis Media (AOM)

Treatment of AOM caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *S. pyogenes*.

When anti-infectives indicated, AAP recommends high-dose amoxicillin or amoxicillin and clavulanate as drugs of choice for initial treatment of AOM; certain cephalosporins (cefdinir, cefpodoxime, cefuroxime, ceftriaxone) recommended as alternatives for initial treatment in penicillin-allergic patients without a history of severe and/or recent penicillin-allergic reactions.

Pharyngitis and Tonsillitis

Treatment of pharyngitis and tonsillitis caused by *S. pyogenes* (group A β-hemolytic streptococci). Generally effective in eradicating *S. pyogenes* from nasopharynx; efficacy in prevention of subsequent rheumatic fever not established.

AAP, IDSA, AHA, and others recommend a penicillin regimen (10 days of oral penicillin V or oral amoxicillin or single dose of IM penicillin G benzathine) as treatments of choice for *S. pyogenes* pharyngitis and tonsillitis; other anti-infectives (oral cephalosporins, oral macrolides, oral clindamycin) recommended as alternatives in penicillin-allergic patients.

If an oral cephalosporin used, 10 day regimen of first generation cephalosporin (cefadroxil, cephalexin) preferred instead of other cephalosporins with broader spectrums of activity (e.g., cefaclor, cefdinir, cefixime, cefpodoxime, cefuroxime).

Bone and Joint Infections

Parenteral treatment of bone and joint infections caused by susceptible *Staphylococcus aureus* (including penicillinase-producing strains).

Meningitis

Parenteral treatment of meningitis caused by susceptible *S. pneumoniae*, *H. influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, or *S. aureus* (including penicillinase-producing strains).

Not a drug of choice for meningitis; treatment failures have been reported, especially in meningitis caused by *H. influenzae*. In addition, bacteriologic response to cefuroxime appears to be slower than that reported with ceftriaxone, which may increase the risk for hearing loss and neurologic sequelae. When a cephalosporin is indicated for the treatment of bacterial meningitis, a parenteral third generation cephalosporin (usually ceftriaxone or cefotaxime) generally recommended.

Respiratory Tract Infections

Treatment of acute maxillary sinusitis caused by susceptible *S. pneumoniae* or *H. influenzae* (non-β-lactamase-producing strains only). Data insufficient to date to establish efficacy for treatment of acute maxillary sinusitis known or suspected to be caused by β-lactamase-producing strains of *H. influenzae* or *M. catarrhalis*. Because of variable activity against *S. pneumoniae* and *H. influenzae*, IDSA no longer recommends second or third generation oral cephalosporins for empiric monotherapy of acute bacterial sinusitis. Oral amoxicillin or amoxicillin and clavulanate usually recommended for empiric treatment. If an oral cephalosporin used as an alternative in children (e.g., in penicillin-allergic individuals), combination

regimen that includes a third generation cephalosporin (cefixime or cefpodoxime) and clindamycin (or linezolid) recommended.

Treatment of secondary bacterial infections of acute bronchitis caused by susceptible *S. pneumoniae*, *H. influenzae* (non-β-lactamase-producing strains only), or *H. parainfluenzae* (non-β-lactamase-producing strains only).

Treatment of acute exacerbations of chronic bronchitis caused by susceptible *S. pneumoniae*, *H. influenzae* (non-β-lactamase-producing strains only), or *H. parainfluenzae* (non-β-lactamase-producing strains only).

Parenteral treatment of lower respiratory tract infections (including pneumonia) caused by susceptible *S. pneumoniae*, *S. aureus* (including penicillinase-producing strains), *S. pyogenes* (group A β-hemolytic streptococci), *H. influenzae* (including ampicillin-resistant strains), *Escherichia coli*, or *Klebsiella*.

Treatment of community-acquired pneumonia (CAP). Recommended by ATS and IDSA as an alternative for treatment of CAP caused by penicillin-susceptible *S. pneumoniae*. Also recommended as an alternative in certain combination regimens used for empiric treatment of CAP. Select regimen for empiric treatment of CAP based on most likely pathogens and local susceptibility patterns; after pathogen is identified, modify to provide more specific therapy (pathogen-directed therapy).

For empiric *outpatient* treatment of CAP when risk factors for drug-resistant *S. pneumoniae* are present (e.g., comorbidities such as chronic heart, lung, liver, or renal disease, diabetes, alcoholism, malignancies, asplenia, immunosuppression; use of anti-infectives within the last 3 months), ATS and IDSA recommend monotherapy with a fluoroquinolone active against *S. pneumoniae* (moxifloxacin, gemifloxacin, levofloxacin) or, alternatively, a combination regimen that includes a β-lactam active against *S. pneumoniae* (high-dose amoxicillin or fixed combination of amoxicillin and clavulanic acid or, alternatively, ceftriaxone, cefpodoxime, or cefuroxime) given in conjunction with a macrolide (azithromycin, clarithromycin, erythromycin) or doxycycline. Cefuroxime and cefpodoxime may be less active against *S. pneumoniae* than amoxicillin or ceftriaxone.

If a parenteral cephalosporin is used as an alternative to penicillin G or amoxicillin for treatment of CAP caused by penicillin-susceptible *S. pneumoniae*, ATS and IDSA recommend ceftriaxone, cefotaxime or cefuroxime; if an oral cephalosporin is used for treatment of these

infections, ATS and IDSA recommend cefpodoxime, cefprozil, cefuroxime, cefdinir, or cefditoren.

Septicemia

Parenteral treatment of septicemia caused by susceptible *S. aureus* (including penicillinase-producing strains), *S. pneumoniae*, *E. coli*, *H. influenzae* (including ampicillin-resistant strains), or *Klebsiella*.

In the treatment of known or suspected sepsis or the treatment of other serious infections when the causative organism is unknown, concomitant therapy with an aminoglycoside may be indicated pending results of in vitro susceptibility tests.

Skin and Skin Structure Infections

Oral treatment of uncomplicated skin and skin structure infections caused by susceptible *S. aureus* (including β-lactamase-producing strains) or *S. pyogenes*.

Parenteral treatment of skin and skin structure infections caused by susceptible *S. aureus* (including β-lactamase-producing strains), *S. pyogenes*, *E. coli*, *Klebsiella*, or *Enterobacter*.

Urinary Tract Infections (UTIs)

Oral treatment of uncomplicated UTIs caused by susceptible *E. coli* or *K. pneumoniae*.

Parenteral treatment of UTIs caused by susceptible *E. coli* or *K. pneumoniae*.

Gonorrhea and Associated Infections

Has been used orally or parenterally for treatment of uncomplicated urethral, endocervical, or rectal gonorrhea caused by susceptible *Neisseria gonorrhoeae*.

Has been used parenterally for treatment of disseminated gonococcal infections caused by susceptible *N. gonorrhoeae*.

Not included in current CDC recommendations for gonococcal infections.

Because of concerns related to recent reports of *N. gonorrhoeae* with reduced susceptibility to cephalosporins, CDC states that oral cephalosporins no longer recommended as first-line treatment for uncomplicated gonorrhea. For treatment of uncomplicated urogenital, anorectal, or pharyngeal gonorrhea, CDC recommends a combination regimen that includes a single dose of IM ceftriaxone *and* either a single dose of oral azithromycin or 7-day regimen of oral doxycycline.

Lyme Disease

Treatment of early Lyme disease manifested as erythema migrans. IDSA, AAP, and other clinicians recommend oral doxycycline, oral amoxicillin, or oral cefuroxime axetil as first-line therapy for treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic involvement or advanced atrioventricular (AV) heart block.

Treatment of early neurologic Lyme disease‡ [off-label] in patients with cranial nerve palsy alone without evidence of meningitis (i.e., those with normal CSF examinations or those for whom CSF examination is deemed unnecessary because there are no clinical signs of meningitis). Parenteral anti-infectives (IV ceftriaxone, IV penicillin G sodium, or IV cefotaxime) recommended for treatment of early Lyme disease when there are acute neurologic manifestations such as meningitis or radiculopathy.

Treatment of Lyme carditis‡ [off-label]. IDSA and others state that patients with AV heart block and/or myopericarditis associated with early Lyme disease may be treated with an oral regimen (doxycycline, amoxicillin, or cefuroxime axetil) or a parenteral regimen (IV ceftriaxone or, alternatively, IV cefotaxime or IV penicillin G sodium). A parenteral regimen usually recommended for initial treatment of hospitalized patients; an oral regimen can be used to complete therapy and for the treatment of outpatients.

Treatment of borrelial lymphocytoma‡ [off-label]. Although experience is limited, IDSA states that available data indicate that borrelial lymphocytoma may be treated with an oral regimen (doxycycline, amoxicillin, or cefuroxime axetil).

Treatment of uncomplicated Lyme arthritis‡ [off-label] without clinical evidence of neurologic disease. An oral regimen (doxycycline, amoxicillin, or cefuroxime axetil) can be used, but a parenteral regimen (IV ceftriaxone or, alternatively, IV cefotaxime or IV penicillin G sodium) should be used in those with Lyme arthritis and concomitant neurologic disease. Patients with persistent or recurrent joint swelling after a recommended oral regimen

should receive retreatment with the oral regimen or a switch to a parenteral regimen. Some clinicians prefer retreatment with an oral regimen for those whose arthritis substantively improved but did not completely resolve; these clinicians reserve parenteral regimens for those patients whose arthritis failed to improve or worsened. Allow several months for joint inflammation to resolve after initial treatment before an additional course of anti-infectives is given.

Perioperative Prophylaxis

Perioperative prophylaxis in patients undergoing cardiac surgery; a drug of choice for cardiac procedures (e.g., coronary artery bypass, pacemaker or other cardiac device insertion, ventricular assist devices).

Perioperative prophylaxis in patients undergoing clean head and neck surgery involving placement of prosthesis (excluding tympanostomy); perioperative prophylaxis in conjunction with metronidazole in patients undergoing clean-contaminated cancer surgery of the head and neck or other clean-contaminated head and neck procedures (excluding tonsillectomy and functional endoscopic sinus procedures). A drug of choice.

Has been used for perioperative prophylaxis in patients undergoing noncardiac thoracic surgery, GI or biliary tract surgery, gynecologic or obstetric surgery (e.g., vaginal hysterectomy), orthopedic procedures, or heart transplantation. Other anti-infectives (e.g., cefazolin) usually preferred.

4.2 Posology and method of administration

Posology

The usual course of therapy is seven days (may range from five to ten days).

Table 1. Adults and children (≥40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acutebacterial sinusitis	250 mg twice daily
Acute otitis media	500 mg twice daily
Acute exacerbations of chronic bronchitis	500 mg twice daily
Cystitis	250 mg twice daily
Pyelonephritis	250 mg twice daily
Uncomplicated skin and soft tissue infections	250 mg twice daily

Lyme disease	500 mg twice daily for 14 days (range 21 days)

Table 2. Children (<40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mgtwice daily
Children aged two years or older with otitis media or, where appropriate, with more severe infections	15 mg/kg twice daily to a maximum of 250 mgtwice daily
Cystitis	15 mg/kg twice daily to a maximum of 250

ly	
Pyelonephritis	15 mg/kg twice daily to a maximum daily for 10 to 14 days
Uncomplicated skin and soft tissue infections	15 mg/kg twice daily to a maximum daily
Lyme disease	15 mg/kg twice daily to a maximum daily for 14 days (10 to 21 days)

There is no experience of using Cefuroxime axetil in children under the age of 3 months.

Renal impairment

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been
established.

Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis

Table 3. Recommended doses for Cefuroxime axetil *in renal impairment*

Creatinine clearance	T1/2 (hrs)	Recommended dosage
≥30 mL/min/1.73 m2	1.4–2.4	no dose adjustment necessary (standard 125 mg to 500 mg given twice daily)
10-29 mL/min/1.73 m2	4.6	standard individual dose given every 24 ho
<10 mL/min/1.73 m2	16.8	standard individual dose given every 48 ho
Patients on haemodialysis	2–4	a further standard individual dose should at the end of each dialysis

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Method of administration Oral use

Cefuroxime axetil tablets should be taken after food for optimum absorption. Cefuroxime axetil tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children Cefuroxime axetil oral suspension may be
used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of betalactam antibacterial agent (penicillins, monobactams and carbapenems)

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (SCARS)

Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn

immediately and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of cefuroxime, treatment with cefuroxime must not be restarted in this patient at any time.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi.* Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease (see section 4.8).

Overgrowth of non-susceptible microorganisms

As with other antibiotics, use of cefuroxime axetil may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).

Antibacterial agent– associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime (see section 4.8). Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given (see section 4.8).

Interference with diagnostic tests

The development of a positive Coombs' Test associated with the use of cefuroxime may interfere with cross matching of blood (see section 4.8).

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil.

Cefuroxime 250/500 mg tablets contain sodium.

This medicinal product contains less than 1 mmol sodium (23 mg) per coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR

4.6 Pregnancy and Lactation

Pregnancy

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of cefuroxime axetil on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

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, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects

The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data from large clinical studies 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 <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not available. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised 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 and not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not known
Infections and infestations	Candida overgrowth		Clostridium difficile overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coombs' test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Cardiac disorders			Kounis syndrome

Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, severe cutaneous adverse reactions (SCARs), including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (exanthematic necrolysis) (TEN) , drug reaction with eosinophilia and systemic symptoms (DRESS), and angioneurotic oedema
Description of selected adverse reactions Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes have been observed which are usually reversible.			

Paediatric population

The safety profile for cefuroxime axetil in children is consistent with the profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorization of the

medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal products. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board

Pharmacovigilance Electronic Reporting System (PvERS);

https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see sections 4.2 and 4.4).

Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins, ATC-Code: J01DC02

Mechanism of action

Cefuroxime axetil undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime.

Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance

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

• hydrolysis by beta-lactamases; including (but not limited to) by extended-spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria species;

• reduced affinity of penicillin-binding proteins for cefuroxime;

• outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria;

• bacterial efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime.

Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

Cefuroxime axetil breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microorganism	Breakpoints (mg/L)	
	S	**R**
Enterobacteriaceae [1, 2]	≤ 8	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤ 0.25	>0.5
Moraxella catarrhalis	≤ 0.125	>4
Haemophilus influenzae	≤ 0.125	>1
Non-species related breakpoints[1]	IE[5]	IE[5]

[1] The cephalosporin breakpoints for *Enterobacteriaceae* will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.
[2] Uncomplicated UTI (cystitis) only (see section 4.1).
[3] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.
[4] The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.
[5] insufficient evidence that the species in question is a good target for therapy with the drug.
An MIC with a comment but without an accompanying S or R-categorization may be reported.

S=susceptible, R=resistant

Microbiological susceptibility

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 cefuroxime axetil in at least some types of infections is questionable.

Cefuroxime is usually active against the following microorganisms *in vitro*.

Commonly susceptible species
Gram-positive aerobes: *Staphylococcus aureus* (methicillin-susceptible)* *Coagulase negative staphylococcus* (methicillin susceptible) *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Spirochaetes: *Borrelia burgdorferi*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus* spp. (other than *P. vulgaris)* *Providencia* spp.
Gram-positive anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Gram-negative anaerobes: *Fusobacterium* spp. *Bacteroides* spp.
Inherently resistant microorganisms

Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium*
Gram-negative aerobes: *Acinetobacter* spp. *Campylobacter* spp. *Morganella morganii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia marcescens*
Gram-negative anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

* All methicillin-resistant *S. aureus* are resistant to cefuroxime.

5.2 Pharmacokinetic properties

Absorption

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal.

Following administration of cefuroxime axetil tablets peak serum levels (2.9 µ g/mL for a 125 mg dose, 4.4 µ g/mL for a 250 mg dose, 7.7 µ g/mL for a 500 mg dose and 13.6 µ g/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with food. The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution

Protein binding has been stated as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV%=28%). Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial

fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised

Elimination

The serum half-life is between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 mL/min/1.73 m^2.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females.

Elderly

No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly (see section 4.2).

Paediatric population

In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults.

There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

Renal impairment

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established.

Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <30 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). Cefuroxime is effectively removed by dialysis.

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

PK/PD relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on 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

Excipient	Specification
Sodium Lauryl Sulfate	USP
Colloidal Silicon Dioxide	USP
Croscarmellose Sodium (Ac-di-sol)	USP
Carboxy methyl Cellulose Calcium	USP
Crospovidone XL 10	USP
Microcrystalline Cellulose (PH-112)	USP
Magnesium Stearate	USP
Talc	USP
Hydroxy Propyl Methyl Cellulose (Hypromellose)	USP

Titanium Dioxide	USP
Poly Ethylene Glycol 6000	USP
Isopropyl Alcohol	USP
Methylene Chloride	USP

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store at a temperature below 30˚C, protect from light and moisture.

6.5 Nature and Content of container

10 tablets packed in Alu-Alu blister and such one Alu-Alu blister packed in a printed mono carton with pack insert.
Pack Size: 1 x 10 Tablets

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Company name: GALPHA LABORATORIES LIMITED
Address: E-221, Kanakia Zillion,
Junction of LBS & CST Road, BKC Annexe,
Kurla West, Mumbai - 400 070.
Country: India
Telephone No.: +91 22 3040 0999
Telefax No.: +91 22 3040 0900
E-mail : sachin.misal@galpha.com & info@galpha.com

8. Marketing Authorization Number

CTD11070 Restum 250mg
CTD11071 Restum 500mg

9. Date of first authorization/renewal of the authorization

3/10/2024

10. Date of revision of the text

11/05/2025