For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TORFUR

(Cefuroxime Axetil Tablets I.P)

COMPOSITION

Torfur 250

Each film coated tablet contains: Cefuroxime Axetil I.P. equivalent to
Cefuroxime ……250mg
Colour: Titanium Dioxide I.P.

Torfur 500

Each film coated tablet contains: Cefuroxime Axetil I.P. equivalent to
Cefuroxime ……..500mg
Colour: Titanium Dioxide I.P.

DOSAGE FORM

Film coated tablet

INDICATION

Cefuroxime axetil Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Pharyngitis/Tonsillitis caused by Streptococcus pyogenes. Cefuroxime axetil Tablets are generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of Streptococcus pyogenes.

Acute Bacterial Otitis Media caused by Streptococcus pneumoniae, Haemophilusinfluenzae (including beta-lactamase-producing strains), Moraxella catarrhalis (including beta-lactamase-producing strains), or Streptococcus pyogenes.

Acute Bacterial Maxillary Sinusitis caused by Streptococcus pneumoniae or Haemophilusinfluenzae (non-beta-lactamase-producing strains only).

Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis caused by Streptococcus pneumoniae, Haemophilusinfluenzae (beta-lactamase negative strains), or Haemophilusparainfluenzae (beta-lactamase negative strains).

Uncomplicated Skin and Skin-Structure Infections caused by Staphylococcus aureus (including beta-lactamase-producing strains) or Streptococcus pyogenes.

Uncomplicated Urinary Tract Infections caused by Escherichia coli or Klebsiellapneumoniae.
Uncomplicated Gonorrhea, urethral and endocervical, caused by penicillinase-producing andnon-penicillinase-producing strains of Neisseria gonorrhoeae and uncomplicated gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of Neisseria gonorrhoeae.

Early Lyme Disease (erythema migrans) caused by Borreliaburgdorferi

DOSE AND METHOD OF ADMINISTRATION

POPULATION/INFECTION	**DOSAGE**	**DURATION (DAYS)**
Adolescents and Adults (13 years and older)		
Pharyngitis/tonsillitis	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10
Acute bacterial exacerbations of chronic bronchitis	250 or 500 mg b.i.d.	10
Secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d.	5-10
Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d.	10
Uncomplicated urinary tract infections	250 mg b.i.d.	7-10
Uncomplicated gonorrhea	1,000 mg once	single dose
Early Lyme disease	500 mg b.i.d.	20
Pediatric Patients (who can swallow tablets whole) 5-12 years		
Acute otitis media	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10

Children under 5 years of age:
Cefuroxime axetil tablets are not suitable for use in children under the age of 5. For patients in this age group it is advised to use an oral suspension. There is no experience in children under 3 months of age.

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 recommendedthat the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectivelyremoved by dialysis.

Table. Recommended doses for cefuroxime axetil in renal impairment

Creatinine clearance	**$T_{½}$ (hrs)**	**Recommended dosage**
≥30 mL/min/1.73 m^2	1.4–2.4	no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 mL/min/1.73 m^2	4.6	standard individual dose given every 24 hours
<10 mL/min/1.73 m^2	16.8	standard individual dose given every 48 hours
Patients on haemodialysis	2–4	a further standard individual dose should be given at the end of each dialysis

Hepatic impairment
There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by thekidney, 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 swallowtablets.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmfuleffects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime should beprescribed 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 mighthave to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroximeshould 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 haveshown no effects on fertility.

CONTRAINDICATIONS

- Hypersensitivity to cefuroxime or to any of the excipients.
- 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).

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactamantibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial agents, serious andoccasionally fatal hypersensitivity reactions have been reported. 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 hypersensitivityreactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used ifcefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It resultsdirectly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete*Borreliaburgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence ofantibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

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

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 inpatients with diarrhoea during or subsequent to the administration of cefuroxime. Discontinuation oftherapy with cefuroxime and the administration of specific treatment for *Clostridium difficile*should be considered.Medicinal products that inhibit peristalsis should not be given.

Interference with diagnostic tests

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood.

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

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 medicinemay cause dizziness, patients should be warned to be cautious when driving or operating machinery.

DRUG INTERACTIONS

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

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combinedoral contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicid is notrecommended. Concurrent administration of probenecid significantly increases the peakconcentration, area underthe serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR.

UNDESIRABLE EFFECTS

The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinaldisturbances 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 ofadverse 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 determinedusing post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data werenot 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 ofdecreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequencyand 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 < 1/10,000and 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 Coomb's test, thrombocytopenia,	haemolyticanaemia

		leukopenia (sometimes profound)	
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
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, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematicnecrolysis) (*see Immune system disorders*), angioneuroticoedema
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 haemolyticanaemia. 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.

OVERDOSE
Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma.Symptoms ofoverdose can occur if the dose is not reduced appropriately in patients with renal impairment.Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
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 resultsin 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 tocefuroxime.

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

Cefuroxime axetil breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on AntimicrobialSusceptibility 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
Haemophilusinfluenzae	≤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.

[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 susceptability of beta-haemolytic streptococci groups A, B, C and G isinferred 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 localinformation on resistance is desirable, particularly when treating severe infections. As necessary, expert adviceshould be sought when the local prevalence of resistance is such that the utility of cefuroxime axetil in at least sometypes of infections is questionable.

Cefuroxime is usually active against the following microorganisms in vitro.

Commonly susceptible species
Gram-positive aerobes: *Staphylococcus aureus* (methicillin susceptible)* *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilusinfluenzae* *Haemophilusparainfluenzae* *Moraxella catarrhalis*
Spirochaetes: *Borreliaburgdorferi*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacterfreundii* *Enterobacteraerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiellapneumoniae* *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. *Morganellamorganii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratiamarcescens*
Gram-negative anaerobes: *Bacteroidesfragilis*
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

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

Pharmacokinetic properties

Absorption

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

Following administration of cefuroxime axetil tablets peak serum levels (2.9 μg/mL for a 125 mg dose, 4.4 μg/mL for a250 mg dose, 7.7 μg/mL for a 500 mg dose and 13.6 μg/mL for a 1000 mg dose) occur approximately 2.4 hours afterdosing when taken with food. The rate of absorption of cefuroxime from the suspension is reduced compared with thetablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17% less). Cefuroximeaxetil oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults and therefore isnot substitutable on a milligram-per-milligram basis.The pharmacokinetics of cefuroxime is linearover the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of250 to 500 mg.

Distribution

Protein binding has been stated as 33 to 50% depending on the methodology used. Following a single dose ofcefuroxime 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 inthe tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputumand 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 normalmaximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose shouldbe adjusted in accordance with the renal function in the elderly.

Paediatrics

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

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

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by thekidney, 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 hasbeen shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above theminimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

Preclinical safety data

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

Gamma glutamyltranspeptidase activity in rat urine is inhibited by various cephalosporins, however the level ofinhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

EXPIRY DATE

Do not use later than the date of expiry.

PACKAGING INFORMATION

Torfur 250 is available as strip pack of 10 tablets
Torfur 500 is available as strip pack of 10 tablets

STORAGE AND HANDLING INSTRUCTIONS

Store below 25°c in a dry place. Protect from light.

MARKETED BY

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IN/TORFUR/250,500mg/Apr-2015/01/PI