Nowcef
(Cefixime)

ناؤسیف کیپسولز اور سسپنشن
(سیفکزیم)
۴۰۰ ملی گرام کیپسول،
۱۰۰ ملی گرام/۵ ملی لیٹر اور ۲۰۰ ملی گرام/۵ ملی لیٹر سسپنشن

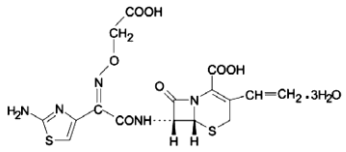
Cefixime Capsules 400mg
Cefixime 100mg/5mL Powder for Oral Suspension
Cefixime 200mg/5mL DS Powder for Oral Suspension

1 DESCRIPTION

Cefixime is a semisynthetic, cephalosporin antibacterial for oral administration. Chemically, it is (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2ene-2-carboxylic acid, 7^2-(Z)-[O-(carboxy methyl) oxime] trihydrate.

Molecular weight = 507.50 as the trihydrate. Chemical Formula is $C_{16}H_{15}N_5O_7S_2.3H_2O$

The structural formula for cefixime is:



2. INDICATIONS AND USAGE

To reduce the development of drug resistant bacteria and maintain the effectiveness of Nowcef (cefixime) and other antibacterial drugs, Nowcef should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
Nowcef (cefixime) is a cephalosporin antibacterial indicated in the treatment of adults and pediatric patients six months of age or older with the following infections when caused by susceptible isolates of the designated bacteria:

2.1 Uncomplicated Urinary Tract Infections

Uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis.

2.2 Otitis Media

Otitis Media caused by *Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pyogenes.* (Efficacy for Streptococcus pyogenes in this organ system was studied in fewer than 10 infections.)
Note: For patients with otitis media caused by Streptococcus pneumoniae, overall response was approximately 10% lower for cefixime than for the comparator. **[See CLINICAL STUDIES (14)]**

2.3 Pharyngitis and Tonsillitis

Pharyngitis and Tonsillitis caused by Streptococcus pyogenes. (Note: Penicillin is the usual drug of choice in the treatment of Streptococcus pyogenes infections. Nowcef is generally effective in the eradication of Streptococcus pyogenes from the nasopharynx; however, data establishing the efficacy of Nowcef in the subsequent prevention of rheumatic fever is not available.)

2.4 Acute Exacerbations of Chronic Bronchitis

Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae and Haemophilus influenzae.*

1.5 Uncomplicated Gonorrhea (cervical/urethral)
Uncomplicated Gonorrhea (cervical/urethral) caused by Neisseria gonorrhoeae (penicillinase-and non-penicillinase-producing isolates).

3 DOSAGE AND ADMINISTRATION

3.1 Adults

The recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg Capsule or capsule daily or the 400 mg Capsule may be split and given as one-half Capsule every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended. The capsule and Capsule may be administered without regard to food.
In the treatment of infections due to Streptococcus pyogenes, a therapeutic dosage of cefixime should be administered for at least 10 days.

3.2 Pediatric Patients (6 months or older)

The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

PEDIATRIC DOSAGE CHART

		100 mg/5 mL	200 mg/5 mL
Patient Weight (kg)	**Dose/Day (mg)**	**Dose/Day (mL)**	**Dose/Day (mL)**
5 to 6.2	50	2.5	1.25
6.3 to 12.5	100	5	2.5
12.6 to 18.8	150	7.5	3.75
18.9 to 25	200	10	5
25.1 to 31.3	250	12.5	6.25
31.4 to 37.5	300	15	7.5
37.6 to 43.8	350	17.5	8.75
43.9 to 50	400	20	10

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical trials of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the Capsule when administered at the same dose.

Therefore, the Capsule or capsule should not be substituted for the suspension in the treatment of otitis media. **[See CLINICAL PHARMACOLOGY (12.3)]**

In the treatment of infections due *to Streptococcus pyogenes,* a therapeutic dosage of cefixime should be administered for at least 10 days.

3.3 Renal Impairment

Nowcef may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Patients whose clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given
6.5 ml of Nowcef for Oral Suspension (200 mg/5 mL) daily or 13 ml of Nowcef for Oral Suspension (100 mg/5 mL) daily. Patients whose clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given 200 mg daily (i.e. half of the 400 mg Capsule). Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

3.4 Reconstitution Directions for Oral Suspension

Directions for Preparing Oral Suspension
Fill previously boiled and cooled water up to the line mark on the bottle and shake vigorously.
The reconstituted suspension can be used for up to 7 days, when stored at room temperature and up to 14 days when refrigerated. without significant loss of potency. Keep tightly closed. Shake well before using.
Discard unused portion after 14 days.

4 DOSAGE FORMS AND STRENGTHS

Nowcef is available for oral administration in the following dosage forms and strengths:

- Capsules provide 400 mg of cefixime as trihydrate. These are size “00” capsules with purple color body & off white cap contain off-white to granular powder.

- Powder for oral suspension, when reconstituted, provides either 100 mg/5 mL or 200 mg/5 mL of cefixime as trihydrate. The powder has an off white to pale yellow color and is strawberry flavored.

5 CONTRAINDICATIONS

Nowcef (cefixime) is contraindicated in patients with known allergy to cefixime or other cephalosporins.

6 WARNINGS AND PRECAUTIONS

6.1 Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Before therapy with Nowcef is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to

penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Nowcef occurs, discontinue the drug.

6.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Nowcef, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

6.3 Dose Adjustment in Renal Impairment

The dose of Nowcef should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully **[See DOSAGE AND ADMINISTRATION (2)].**

6.4 Coagulation Effects

Cephalosporins, including Nowcef, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

6.5 Development of Drug-Resistant Bacteria

Prescribing Nowcef (cefixime) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

7 ADVERSE REACTIONS

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly seen adverse reactions in U.S. trials of the Capsule formulation were gastrointestinal events, which were reported in 30% of adult patients on either the twice daily or the once daily regimen. Five percent (5%) of patients in the U.S. clinical trials discontinued therapy because of drug-related adverse reactions. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving Capsules.

7.2 Post-marketing Experience

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%).

Gastrointestinal

Several cases of documented pseudomembranous colitis were identified in clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rshes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic

Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal

Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System

Headaches, dizziness, seizures.

Hemic and Lymphatic System

Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.

Abnormal Laboratory Tests

Hyperbilirubinemia.

Other Adverse Reactions

Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

Adverse Reactions Reported for Cephalosporin-class Drugs

Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. [See **DOSAGE AND ADMINISTRATION (2)** and **OVERDOSAGE (10)]** If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

8 DRUG INTERACTIONS

8.1 Carbamazepine

Elevated carbamazepine levels have been reported in post-marketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

8.2 Warfarin and Anticoagulants

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

9.2 Labor and Delivery

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

9.3 Nursing Mothers

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

9.4 Pediatric Use

Safety and effectiveness of cefixime in children aged less than six months old have not been established. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving Capsules.

9.5 Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A pharmacokinetic study in the elderly detected differences in pharmacokinetic parameters [See **CLINICAL PHARMACOLOGY (12.2)].** These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.

9.6 Renal Impairment
The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully [See DOSAGE AND ADMINISTRATION (2.3)].

10 OVERDOSAGE
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

11 CLINICAL PHARMACOLOGY
11.1 Mechanism of Action

Cefixime is a semisynthetic cephalosporin antibacterial drug [see **Microbiology** (12.4)].

11.2 Pharmacokinetics
Nowcef Capsule and suspension, given orally, are about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200 mg Capsule of cefixime produces an average peak serum concentration of approximately 2 mcg/mL (range 1 to 4 mcg/mL); a single 400 mg Capsule produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The oral suspension produces average peak concentrations approximately 25% to 50% higher than the Capsules, when tested in normal adult volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to7.7 mcg/mL), respectively, when tested in normal adult volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the Capsule after doses of 100 to 400 mg, when tested in normal adult volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the Capsule. Because of the lack of bioequivalence, Capsules should not be substituted for oral suspension in the treatment of otitis media **[See DOSAGE AND ADMINISTRATION (2)].** Crossover studies of Capsule versus suspension have not been performed in children.
The 400 mg capsule is bioequivalent to the 400 mg Capsule under fasting conditions. However, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on C_{max}.
Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg Capsule, a single 400 mg Capsule or 400 mg of cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension. Peak serum concentrations occur between 3 and 8 hours following oral administration of a single 400 mg capsule.

Distribution
Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the Capsule or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. Adequate data on CSF levels of cefixime are not available.

Metabolism and Excretion
There is no evidence of metabolism of cefixime in vivo. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours but may range up to 9 hours in some normal volunteers.

Special Populations
Geriatrics: Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults. Differences in the pharmacokinetic parameters between 12 young and 12 elderly subjects who received 400 mg of cefixime once daily for 5 days are summarized as follows:

Pharmacokinetic Parameters (mean ± SD) for Cefixime in Both Young & Elderly Subjects

Pharmacokinetic parameter	Young	Elderly
C_{max} (mg/L)	4.74 ± 1.43	5.68 ± 1.83
T_{max} (h)*	3.9 ± 0.3	4.3 ± 0.6
AUC (mg.h/L)*	34.9 ± 12.2	49.5 ± 19.1
$T_{½}$ (h)*	3.5 ± 0.6	4.2 ± 0.4
C_{ave} (mg/L)*	1.42 ±0.50	1.99 ± 0.75

*Difference between age groups was significant. (p<0.05)

However, these increases were not clinically significant [See **DOSAGE AND ADMINISTRATION** (2)].

Renal Impairment: In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21 to 60 mL/min.

11.3 Microbiology
Mechanism of Action Bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime has been shown to be active against most isolates of the following bacteria both in vitro
and in clinical infections [see **INDICATIONS AND USAGE (1)]:**
Gram-positive bacteria
Streptococcus pneumoniae
Streptococcus pyogenes
Gram-negative bacteria
Haemophilus influenzae
Moraxella catarrhalis
Escherichia coli
Proteus mirabilis
Neisseria gonorrhoeae

The following in vitro data are available, but their clinical significance is unknown. Nowcef exhibits in vitro MICs of 1 mcg/mL or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of Nowcef in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.
Gram-positive bacteria
Streptococcus agalactiae
Gram-negative bacteria
Haemophilus parainfluenzae
Proteus vulgaris
Klebsiella pneumoniae
Klebsiella oxytoca
Pasteurella multocida
Providencia species
Salmonella species
Shigella species
Citrobacter amalonaticus
Citrobacter diversus
Serratia marcescens

12 NONCLINICAL TOXICOLOGY
12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

13 CLINICAL STUDIES
Comparative clinical trials of otitis media were conducted in nearly 400 children between the ages of 6 months to 10 years. Streptococcus pneumoniae was isolated from 47% of the patients, Haemophilus influenzae from 34%, Moraxella catarrhalis from 15% and S. pyogenes from 4%.

The overall response rate of Streptococcus pneumoniae to cefixime was approximately 10% lower and that of Haemophilus influenzae or Moraxella catarrhalis approximately 7% higher (12% when beta-lactamase positive isolates of H. influenzae are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg twice a day or 8 mg/kg once a day, or with a comparator. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had Haemophilus influenzae resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two to Four Weeks Post-Therapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime(a)	Cefixime(a)	Control(a)
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae	17/22 (77%)	9/12 (75%)	1/1 (b)
Moraxella catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S. pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.
(b) An additional 20 beta-lactamase positive isolates of Haemophilus influenzae were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these, the clinical course could be assessed and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

14 STORAGE

Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

15 HOW SUPPLIED

- NOWCEF (Cefixime) Capsules 400mg
  are available in blister packs of 5's.
- NOWCEF (Cefixime) 100mg / 5ml Suspension
  is available in amber glass bottle (30mL after Reconstitution)
- NOWCEF DS (Cefixime) 200mg / 5ml Suspension
  is available in amber glass bottle (30mL after Reconstitution)

16 PATIENT COUNSELING INFORMATION

16.1 Information for Patients

Patients should be counseled that antibacterial drugs, including cefixime, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefixime is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefixime for oral suspension or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ناؤسیف کیپسولز اور سسپنشن

(سیفکسم)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: صرف مستند ڈاکٹر کے نسخہ پر فروخت کی جائے۔

۳۰ ڈگری سے کم درجہ حرارت رکھیں۔ دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

MANUFACTURED BY:
NAWAN LABORATORIES (PVT) LTD.
136, Sector 15, Korangi Industrial Area, Karachi-74900, Pakistan.