**For the use of a Registered Medical Practitioner or a Hospital**

# ADCEF

**(Cefdinir Capsules, 300mg)**

# ADCEF INSTA-USE

**(Cefdinir Oral Suspension 125 mg/5 ml)**

## COMPOSITION

**Adcef**

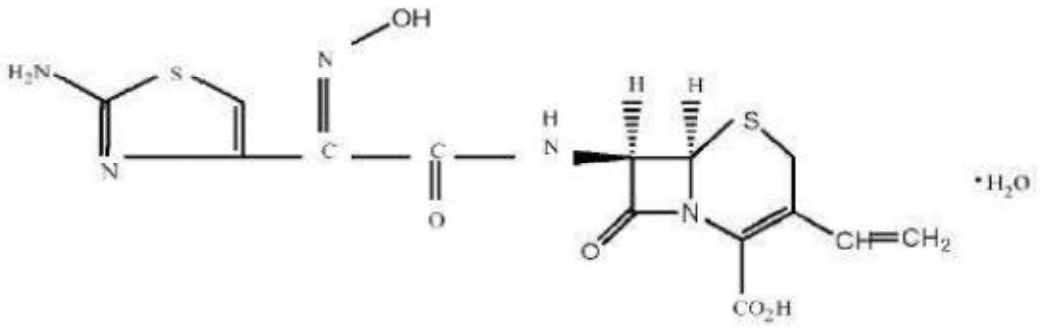
Each hard gelatin capsule contains:
Cefdinir 300 mg

**Adcef Insta-Use**

Each 5 ml oral suspension contains:
Cefdinir 125 mg
in a flavoured base q.s.
Colour : Lake of Quinoline Yellow W.S

## DESCRIPTION

Adcef / Adcef Insta Use contains the active ingredient cefdinir, an extended-spectrum, semisynthetic cephalosporin, for oral administration. Chemically, cefdinir is [6R- [6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl) (hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid. The empirical formula of cefdinir is C14H13N5O5S2 and the molecular weight is 395.42.




## CLINICAL PHARMACOLOGY

***Pharmacokinetics***

**Absorption**

Following administration of a 300mg capsule dose, maximum plasma cefdinir concentration occurs 2-4 hours postdose. Estimated bioavailability of cefdinir capsules is 21%. Food exerts no clinically significant effect on cefdinir bioavailability. Cefdinir does not accumulate in plasma following once or twice daily administration to subjects with normal renal function.

**Distribution**
The mean volume of distribution of cefdinir in adult subjects is 0.35 L/kg (– 0.29). Cefdinir is 60% to 70% bound to plasma proteins; binding is independent of concentration.
Tissue concentration of Cefdinir is as follows:

| Tissue | Concentration | |
|---|---|---|
| | Mg/L | Mg/kg |
| Bronchial Mucosa | 0.78 | 31% |
| Skin blisters | 0.65 | 48% |
| Epithelial lining fluid | 0.29 | 35% |
| Middle ear fluid | 0.21 | 15% |
| Ethmoid and maxillary sinuses | 0.12 | 16% |
| Tonsil tissue | 0.25 | 24% |

**Metabolism and Excretion**
Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug. Cefdinir is eliminated principally via renal excretion with a mean plasma elimination half-life (t1/2) of 1.7 (– 0.6) hours. In healthy subjects with normal renal function, renal clearance is 2.0 (– 1.0) ml/min/kg, and apparent oral clearance is 11.6 (– 6.0) and 15.5 (– 5.4) ml/min/kg following doses of 300 mg and 600 mg, respectively. Mean percent of dose recovered unchanged in the urine following 300 and 600 mg doses are 18.4% (– 6.4) and 11.6% (– 4.6), respectively. Cefdinir clearance is reduced in patients with renal dysfunction.

**Special Populations**
***Patients with Renal Insufficiency***
Decreases in cefdinir elimination rate, apparent oral clearance (CL/F) and renal clearance were approximately proportional to the reduction in creatinine clearance (CLcr). As a result, plasma cefdinir concentrations were higher and persisted longer in subjects with renal impairment than in those without renal impairment. In subjects with CLcr between 30 and 60 ml/min, Cmax and t1/2 increased by approximately 2-fold and AUC by approximately 3-fold. In subjects with CLcr <30 ml/min, Cmax increased by approximately 2-fold, t1/2 by approximately 5-fold, and AUC by approximately 6-fold. Dosage adjustment is recommended in patients with markedly compromised renal function.

***Hemodialysis***
Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination t1/2 from 16 (–3.5) to 3.2 (–1.2) hours. Dosage adjustment is recommended in this patient population.

***Hepatic Disease***
Because cefdinir is predominantly renally eliminated and not appreciably metabolized, studies in patients with hepatic impairment were not conducted. It is not expected that dosage adjustment will be required in this population.

***Geriatric Patients***
Systemic exposure to cefdinir after a single 300mg dose was substantially increased in older subjects, Cmax by 44% and AUC by 86%. This increase was due to a reduction in cefdinir clearance. The apparent volume of distribution was also reduced, thus no appreciable alterations in apparent elimination half-life were observed (elderly: 2.2 – 0.6 hours vs young: 1.8 – 0.4 hours). Since cefdinir clearance has been shown to be primarily related to changes in renal function rather than age, elderly patients do not require dosage adjustment unless they have markedly compromised renal function (creatinine clearance <30 ml/min).

***Gender and Race***
The results of a meta-analysis of clinical pharmacokinetics indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

**Microbiology**
As with other cephalosporins, bactericidal activity of cefdinir results from inhibition of cell wall synthesis. Cefdinir is stable in the presence of some, but not all, b-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

Cefdinir has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections:

***Aerobic Gram-Positive Microorganisms***
Staphylococcus aureus (including b-lactamase producing strains), Streptococcus pneumoniae (penicillin-susceptible strains only), Streptococcus pyogenes. Cefdinir is inactive against methicillin-resistant staphylococci.

***Aerobic Gram-Negative Microorganisms***
Haemophilus influenzae (including b-lactamase producing strains), Haemophilus parainfluenzae (including b-lactamase producing strains), Moraxella catarrhalis (including b-lactamase producing strains).

Cefdinir exhibits in vitro minimum inhibitory concentrations (MICs) of 1 µ g/ml or less against (‡90%) strains of the following microorganisms but their clinical significance is unknown.

***Aerobic Gram-Positive Microorganisms***
Staphylococcus epidermidis (methicillin-susceptible strains only), Streptococcus agalactiae Viridans group streptococci. Cefdinir is inactive against Enterococcus and methicillinresistant Staphylococcus species.

***Aerobic Gram-Negative Microorganisms***
Citrobacter diversus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis. Cefdinir is inactive against Pseudomonas and Enterobacter species.

## INDICATIONS AND USAGE

Adcef / Adcef Insta Use is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

**Community-Acquired Pneumonia** caused by Haemophilus influenzae (including blactamase producing strains), Haemophilus parainfluenzae (including b-lactamase producing strains), Streptococcus pneumoniae (penicillin-susceptible strains only), and Moraxella catarrhalis (including b-lactamase producing strains).

**Acute Exacerbations of Chronic Bronchitis** caused by Haemophilus influenza (including b-lactamase producing strains), Haemophilus parainfluenzae (including blactamase producing strains), Streptococcus pneumoniae (penicillin-susceptible strains only), Moraxella catarrhalis (including b-lactamase producing strains).

**Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes*

**NOTE:** Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

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

**Pediatric Patients**

Adcef Insta Use is indicated for the treatment of patients in the following conditions: ***Pharyngitis/Tonsillitis*** caused by *Streptococcus pyogenes* (**Note:** Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

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

## CONTRAINDICATIONS

Adcef / Adcef Insta Use is contraindicated in patients with known hypersensitivity to cephalosporin class of antibiotics.

## WARNINGS

Before therapy with cefdinir is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefdinir, other cephalosporins, penicillins, or other drugs. If cefdinir is to be given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among b-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 cefdinir occurs, the drug should be discontinued.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

## PRECAUTIONS

### General

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered.

Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis. In patients with transient or persistent renal insufficiency (creatinine clearance <30 ml/min), the total daily dose of Cefdinir should be reduced because high and prolonged plasma concentrations of cefdinir can result, following recommended doses.

## DRUG INTERACTIONS

***Antacids (aluminum- or magnesium-containing)***

Concomitant administration of 300 mg cefdinir capsules with 30 ml antacid suspension reduces the rate (Cmax) and extent (AUC) of absorption by approximately 40%. Time to reach Cmax is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during Cefdinir therapy, Cefdinir should be taken at least 2 hours before or after the antacid.

***Probenecid***

As with other b-lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir plasma levels, and a 50% prolongation in the apparent elimination half-life.

***Iron Supplements and Foods Fortified With Iron***

Concomitant administration of cefdinir with a therapeutic iron supplement containing 60 mg of elemental iron (as $FeSO_4$) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during Cefdinir therapy, Cefdinir should be taken at least 2 hours before or after the supplement.

The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied.

There have been rare reports of reddish stools in patients who have received cefdinir in Japan. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

***Drug/Laboratory Test Interactions***
A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinitest¤ , BenedictÕs solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape ) be used. Cephalosporins are known to occasionally induce a positive direct Coombs test.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***
The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed in vitro in the structural chromosome aberration assay in V79 Chinese hamster lung cells or in vivo in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m2/day).

**Pregnancy - Teratogenic Effects**
***Pregnancy Category B***
Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day or in rabbits at oral doses up to 10 mg/kg/day. Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at ‡100 mg/kg/day, and in rat offspring at ‡32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function. There are, however, 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.

**Labor and Delivery**
Cefdinir has not been studied for use during labor and delivery.

**Nursing Mothers**
Following administration of single 600 mg doses, cefdinir was not detected in human breast milk.

**Pediatric Use**
Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

**Geriatric Use**
Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse

events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised.

## ADVERSE REACTIONS

In clinical trials, in patients treated with cefdinir, most adverse events were mild and self limiting. No deaths or permanent disabilities were attributed to cefdinir.

The most frequently occurring adverse events (‡1%) with Cefdinir 600mg were diarrhea, vaginal moniliasis, nausea, headache, abdominal pain, vaginitis. Incidence of adverse events <1% but >0.1% were rash, dyspepsia, flatulence, vomiting, anorexia, constipation, abnormal stools, asthenia, dizziness, insomnia, leukorrhoea, pruritis and somnolence.

### Laboratory Events

The following clinically significant laboratory changes in clinical trials irrespective of relationship with therapy with cefdinir were reported in ‡1% of patients: increased urine leukocytes, increased urine proteins, increased gamma-glutamyltransferase, decreased and increased lymphocytes, increased microhematuria.

### Cephalosporin Class Adverse Events

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:
Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

## OVERDOSAGE

Information on cefdinir overdosage in humans is not available. In acute rodent toxicity studies, a single oral 5600 mg/kg dose produced no adverse effects. Toxic signs and symptoms following overdosage with other b-lactam antibiotics have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis removes cefdinir from the body. This may be useful in the event of a serious toxic reaction from overdosage, particularly if renal function is compromised.

## DOSAGE AND ADMINISTRATION

### Capsules

The recommended dosage and duration of treatment for infections in adults and adolescents are described in the following chart; the total daily dose for all infections is 600 mg. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in

pneumonia or skin infections; therefore, Adcef should be administered twice daily in these infections. Adcef may be taken without regard to meals.

| **Adults and Adolescents (Age 13 years and Older)** | | |
|---|---|---|
| **Type of Infection Dosage** | **Duration** | |
| Community-Acquired Pneumonia | 300 mg b.i.d | 10 days |
| Acute Exacerbation of Chronic Bronchitis | 300 mg b.i.d or 600mg od | 10 days |
| Pharyngitis/ Tonsillitis | 300 mg b.i.d or 600mg od | 10 days |
| Uncomplicated Skin and Skin Structure Infections | 300 mg b.i.d | |

**Patients with Renal Insufficiency**
For adult patients with creatinine clearance <30 mL/min, the dose of cefdinir should be 300 mg given once daily.

Creatinine clearance is difficult to measure in outpatients. However, the following formula may be used to estimate creatinine clearance (CLcr) in adult patients. For estimates to be valid, serum creatinine levels should reflect steady-state levels of renal function.

Males: $CL_{cr}$ = (weight) (140 - age)
---
(72)(serum creatinine)

Females: CLcr = 0.85 x above value

where creatinine clearance is in ml/min, age is in years, weight is in kilograms, and serum creatinine is in mg/dL.

The following formula may be used to estimate creatinine clearance in pediatric patients.

CLcr = k x body length or height
---
serum creatinine

where, k= 0.55 for pediatric patients older than 1 year and 0.45 for infants (upto 1 year). In the above equation, creatinine clearance is in ml/min/1.73m2; body length or height in centimeters and serum creatinine in mg/dl.

For pediatric patients, a creatinine clearance of <30ml/min/1.73m2, the dose of cefdinir should be 7 mg/kg (upto 300 mg) given once daily.

**Patients on Hemodialysis**
Hemodialysis removes cefdinir from the body. In patients maintained on chronic hemodialysis, the recommended initial dosage regimen is a 300 mg or 7 mg/kg dose every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg) should be given. Subsequent doses (300 mg or 7 mg/kg) are then administered every other day.

**Oral Suspension**
The recommended dosage and duration of treatment for infections in pediatric patients are described in the following chart; the total daily dose for all infections is 14 mg/kg, up to a maximum dose of 600 mg per day. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in skin infections; therefore, Adcef Insta Use should be administered twice daily in this infection. Adcef Insta Use may be administered without regard to meals.

| **Pediatrics (Age 6 months through 12 years)** | | |
|---|---|---|
| **Type of Infection Dosage** | **Duration** | |
| Acute Bacterial Otitis Media | 7 mg/kg b.i.d or 14 mg/kg od | 5-10 days |
| Pharyngitis/ Tonsillitis | 7 mg/kg b.i.d or 14 mg/kg od | 5-10 days |
| Uncomplicated Skin and Skin Structure Infections | 7 mg/kg b.i.d | 10 days |

**Adcef Insta Use pediatric dosage chart**

| Weight | 125 mg/ 5 mL |
|---|---|
| 9 kg/ 20 lbs | 2.5 mL (1/2 tsp) q12h or 5 mL (1 tsp) q24h |
| 18 kg/ 40 lbs | 5 mL (1 tsp) q12h or 10 mL (2 tsp) q24h |
| 27 kg/ 60 lbs | 7.5 mL (11/2 tsp) q12h or 15 mL (3 tsp) q24h |
| 36 kg/ 80 lbs | 10 mL (2 tsp) q12h or 20 mL (4 tsp) q24h |
| 43 kg* /95 lbs | 12 mL (21/2 tsp) q12h or 24 mL (5 tsp) q24h |

* Pediatric patients who weigh 43 kg should receive the maximum daily dose of 600 mg.

**EXPIRY DATE**
Do not use later than expiry date.

**STORAGE**
Store below 25oC, protected from moisture.

**PRESENTATION**
Adcef is available as grey and yellow capsules each containing cefdinir 300 mg. Adcef Insta Use is available as 30 ml bottle containing cefdinir 125 mg /5 ml.

**HOW SUPPLIED**
Adcef: Strip of 10 capsules.
Adcef Insta Use: 30 ml bottle.

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

**IN/ ADCEF 300mg / ADCEF INSTA 125/5ml /Aug-15/01/PI**