For the use of a Registered Medical Practitioner or a Hospital

ADCEF DT

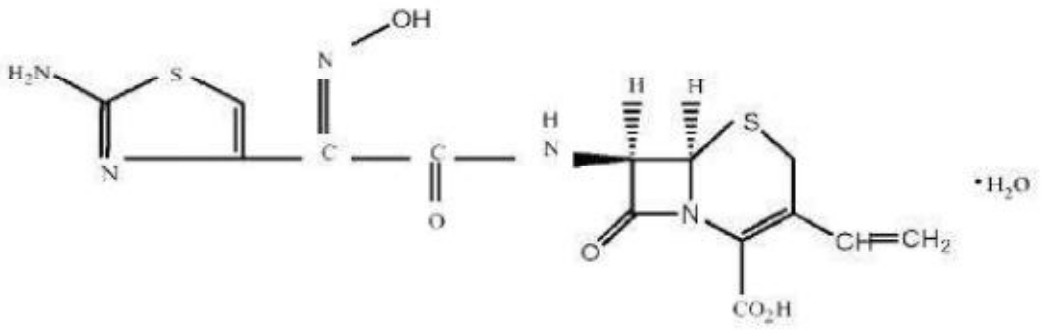
(Cefdinir Kid Tablets)

COMPOSITION

Each Uncoated Dispersible tablet contains:
Cefdinir U.S.P. 125 mg
Colour: Iron Oxide Yellow

DESCRIPTION

Cefdinir is an extended-spectrum, semisynthetic cephalosporin, for oral administration. Chemically, Cefdinir is [6*R*-[6α,7β(Z)]]-(-)- (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5- thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The empirical formula of cefdinir is $C_{14}H_{13}N_5O_5S_2$ and the molecular weight is 395.41.



Cefdinir is a white to light yellow crystalline powder; it is soluble in 0.1 M Phosphate buffer (pH 7) solution, practically insoluble in water, in alcohol and in diethyl ether.

CLINICAL PHARMACOLOGY

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, beta-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 β-lactamase producing strains) NOTE: Cefdinir is inactive against methicillin-resistant staphylococci. *Streptococcus pneumoniae* (penicillin-susceptible strains only) *Streptococcus pyogenes.*

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae (including β-lactamase producing strains) *Haemophilus parainfluenzae* (including β-lactamase producing strains) *Moraxella catarrhalis* (including β-lactamase producing strains) The following *in vitro* data are available, but their clinical significance is unknown. Cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/mL or less against (_ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

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

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

Pharmacokinetics
Absorption:
Oral Bioavailability: Maximal plasma cefdinir concentrations occur 2 to 4 hours postdose following administration. Plasma cefdinir concentrations increase with dose, but the increases are less than dose-proportional from 300 mg (7 mg/kg) to 600 mg (14 mg/kg). Estimated absolute bioavailability of Cefdinir Suspension is 25%. The mean (± SD) plasma cefdinir pharmacokinetic parameter values following administration to pediatric subjects at a dose of 7 mg/kg and 14 mg/kg are approximately as follows: Cmax (μg/ml) - 2.30 (0.65), Tmax (hr) - 2.2 (0.6) & AUC (μg. hr /mL) - 8.31 (2.50) Cmax (μg/ml) - 3.86 (0.62), Tmax (hr) - 1.8 (0.4) & AUC (μg. hr /mL) - 13.4 (2.64) respectively.
Effect of Food: cefdinir may be taken without regard to food.

Distribution : The mean volume of distribution (Vdarea) of cefdinir in adult subjects is 0.35 L/kg (± 0.29); in pediatric subjects (age 6 months-12 years), cefdinir Vdarea is 0.67 L/kg (± 0.38). Cefdinir is 60% to 70% bound to plasma proteins in both adult and pediatric subjects; binding is independent of concentration.

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 and 600 mg, respectively. Mean percent of dose recovered unchanged in the urine following 300 mg and 600 mg doses is 18.4% (± 6.4) and 11.6% (± 4.6), respectively. Cefdinir clearance is reduced in patients with renal dysfunction.

Because renal excretion is the predominant pathway of elimination, dosage should be adjusted in patients with markedly compromised renal function or who are undergoing hemodialysis.

Special Populations:
Hepatic Disease: It is not expected that dosage adjustment will be required in this population.
Gender and Race: The results of a meta-analysis of clinical pharmacokinetics (N = 217) indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

INDICATIONS AND USAGE
Adcef DT 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.

Acute Bacterial Otitis Media caused by *Haemophilus influenza* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-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.

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

CONTRAINDICATIONS
Cefdinir is contraindicated in patients with known allergy to the 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 penicillinsensitive patients, caution should be exercised because crosshypersensitivity among β-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. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. 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 broadspectrum 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 cefdinir 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 β-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. Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. 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®, Benedict's 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.

ADVERSE EVENTS

Most adverse events reported in clinical trials were mild and self limiting. No deaths or permanent disabilities were attributed to cefdinir. Adverse events associated with cefdinir trials in USA in pediatric
patients (N = 1783)a

Incidence 1%	Diarrhoea	8%
	Rash	3%
	Vomiting	1%

Incidence < 1% but > 0.1%	Cutaneous moniliasis	0.8%
	Abdominal pain	0.9%
	Leukopenia[b]	0.8%
	Vaginal moniliasis	0.3% Of girls
	Vaginitis	0.3% Of girls
	Abnormal stools	0.2%
	Dyspepsia	0.2%
	Hyperkinesia	0.2%
	Increased AST[b]	0.2%
	Maculopapular rash	0.2%
	Nausea	0.2%

[a]977 males, 806 females

[b]Laboratory changes were occasionally reported as adverse events.

NOTE: In both cefdinir- and control-treated patients, rates of diarrhea and rash were higher in the youngest pediatric patients. The incidence of diarrhea in cefdinir-treated patients 2 years of age was 17% (95/557) compared with 4% (51/1226) in those > 2 years old. The incidence of rash (primarily diaper rash in the younger patients) was 8% (43/557) in patients 2 years of age compared with 1% (8/1226) in those > 2 years old.
The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US: Laboratory value changes of possible clinical significance observed with cefdinir trials in pediatric patients in USA (N = 1783)

Incidence 1%	Increased Lymphocytes	
	Decreased Lymphocytes	2%, 0.8%
	Decreased Alkaline Phosphatase	1%
	Increased Bicarbonate[a]	1%
	Increased Eosinophils	1%
	Increased Lactate dehydrogenase	1%
	Increased Platelets	1%
	Increased PMNs, Decreased PMNs	1%, 1%
	Increased Urine protein	1%
Incidence <1% but >0.1%	Increased Phosphorus Decreased Phosphorus	0.9%, 0.4%
	Increased Urine pH	0.8%
	Decreased White blood cells	0.7%, 0.3%

	Increased White blood cells	
	Decreased Calcium[a]	0.5%
	Decreased Hemoglobin	0.5%
	Urine leukocytes	0.5%
	Increased Monocytes	0.4%
	Increased AST	0.3%
	Increased Potassium[a]	0.3%
	Increased Urine specific gravity	0.3%, 0.1%
	Decreased Urine specific gravity	
	Decreased Hematocrit[a]	0.2%

[a] N=1387 for these parameters.

OVERDOSAGE

Information on cefdinir overdosage in humans is not available.

DOSAGE AND ADMINISTRATION

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. It may be administered without regard to meals.

Pediatric Patients (Age 6 Months Through 12 Years)

Type of Infection	Dosage	Duration
Acute Bacterial Otitis Media	7 mg/kg q12h or 14 mg/kg q24h	5 to 10 days or 10 days
Acute Maxillary Sinusitis	7 mg/kg q12h or 14 mg/kg q24h	10 days or 10 days
Pharyngitis/Tonsillitis	7 mg/kg q12h 5 to or 14 mg/kg q24h	5 to 10 days or 10 days
Uncomplicated Skin and Skin Structure Infections	7 mg/kg q12h	10 days

Patients with Renal Insufficiency

For pediatric patients, a creatinine clearance of < 30ml/min/1.73 $m^{2,}$ the dose of cefdinir should be 7 mg/kg (upto 300mg) given once daily.

Creatinine clearance is difficult to measure in outpatients. However, the following formula may be used to estimate creatinine clearance (CLcr) 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/1.73 m^2; body length or height in centimeters and serum creatinine in mg/dl.

Direction for use: Disperse the tablet in a tablespoonful of boiled and cooled water before administration.

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store below 25^oC, protected from moisture. Keep all the tablets out of the reach of children.

PRESENTATION
Adcef DT is available in strip of 10 tablets.

MARKETED BY

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

IN/ADCEF DT 125mg/Aug-15/01/PI