National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

RANICEF 125 SUSPENSION

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RANICEF 125 SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Ranicef 125 for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5ml contains Cefdinir 125mg

See section 6.1 for full list of excipients

3. Pharmaceutical Form: Powder for Oral Suspensions

4. Clinical Particulars:

4.1 Therapeutic Indications:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RANICEF 125 and other antibacterial drugs, RANICEF 125 should be used only to treat or prevent 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 antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. RANICEF 125 (cefdinir) capsules and RANICEF 125 (cefdinir) for oral suspension 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.

Adults and Adolescents

Community-Acquired Pneumoniacaused by Haemophilus influenzae (including β-lactamase producing strains), Haemophilus parainfluenzae (including β-lactamase producing strains), Streptococcus pneumoniae (penicillin-susceptible strains only), and Moraxella catarrhalis (including βlactamase producing strains)

Acute Exacerbations of Chronic Bronchitis caused by Haemophilus influenzae (including β-lactamase producing strains), Haemophilus parainfluenzae (including β-lactamase producing strains), Streptococcus pneumoniae (penicillin-susceptible strains only), and Moraxella catarrhalis (including βlactamase producing strains).

Acute Maxillary Sinusitis caused by Haemophilus influenzae (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. 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 β-lactamase producing strains) and Streptococcus pyogenes.

Pediatric Patients Acute Bacterial Otitis Media caused by Haemophilus influenzae (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. 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 β-lactamase producing strains) and Streptococcus pyogenes.

4.2 Posology and method of administration:

Powder for 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, RANICEF 125 for Oral Suspension should be administered twice daily in this infection. RANICEF 125 for Oral Suspension 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 10 days

Acute Maxillary Sinusitis	7 mg/kg q12h or 14 mg/kg q24h	10 days 10 days
Pharyngitis/Tonsillitis	7 mg/kg q12h or 14 mg/kg q24h	5 to 10 days 10 days
Uncomplicated Skin and Skin Structure Infections	7 mg/kg q12h	10 days

RANICEF 125 FOR ORAL SUSPENSION PEDIATRIC DOSAGE CHART

Weight	**125 mg/5 mL**	**250 mg/5 mL**
9 kg/20 lbs	2.5 mL q12h or 5 mL q24h	Use 125 mg/5 mL product
18 kg/40 lbs	5 mL q12h or 10 mL q24h	2.5 mL q12h or 5 mL q24h
27 kg/60 lbs	7.5 mL q12h or 15 mL q24h	3.75 mL q12h or 7.5 mL q24h
36 kg/80 lbs	10 mL q12h or 20 mL q24h	5 mL q12h or 10 mL q24h
__ 43 kg[a]/95 lbs	12 mL q12h or 24 mL q24h	6 mL q12h or 12 mL q24h

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

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.

$$\text{Males: } CLcr = \frac{(\text{weight})\,(140 - \text{age})}{(72)\,(\text{serum creatinine})}$$

Females: CLcr = 0.85 × above value

where creatinine clearance is in mL/min, age is in years, weight is in kilograms, and serum creatinine is in mg/dL.[3] The following formula may be used to estimate creatinine clearance in pediatric patients:

$$CLcr = K \times \frac{\text{body length or height}}{\text{Serum creatinine}}$$

where K = 0.55 for pediatric patients older than 1 year(4) and 0.45 for infants (up to 1 year) [5]

In the above equation, creatinine clearance is in mL/min/1.73 m2, body length or height is in centimeters, and serum creatinine is in mg/dL.

For pediatric patients with a creatinine clearance of < 30 mL/min/1.73 m2, the dose of cefdinir should be 7 mg/kg (up to 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.

Directions for Mixing RANICEF 125 for Oral Suspension

Final Concentration	Final Volume (mL)	Amount of Water	Directions
125 mg/5 mL	60 100	38 Ml 63 mL	Tap bottle to loosen powder, then add water in 2 portions. Shake well after each aliquot.
250 mg/5 mL	60 100	38 mL 63 mL	Tap bottle to loosen powder, then add water in 2 portions. Shake well after each aliquot.

After mixing, the suspension can be stored at room temperature (25°C/77°F). The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be used for 14 days, after which any unused portion must be discarded.

4.3 Contraindications:
RANICEF 125 (cefdinir) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

4.4 Special warning and precaution for use:
BEFORE THERAPY WITH RANICEF 250 (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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including RANICEF 125, 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 strains 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.

PRECAUTIONS

General

Prescribing RANICEF 125 in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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 RANICEF 125 should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses.

Information for Patients
Patients should be counseled that antibacterial drugs including RANICEF 125 should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When RANICEF 125 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 RANICEF 125 or other antibacterial drugs in the future.

Antacids containing magnesium or aluminum interfere with the absorption of cefdinir.
If this type of antacid is required during RANICEF 125 therapy, RANICEF 125 should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during RANICEF 125 therapy, RANICEF 125 should be taken at least 2 hours before or after the supplement. Iron-fortified infant formula does not significantly interfere with the absorption of cefdinir. Therefore, RANICEF 125 for Oral Suspension can be administered with iron-fortified infant formula.

Diabetic patients and caregivers should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

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.

4.5 Interaction with other medicinal products and other forms of interaction:
Antacids (aluminum- or magnesium-containing)
Concomitant administration of 300-mg cefdinir capsules with 30 mL Maalox® TC 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 RANICEF 125 therapy, RANICEF 125 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 t½.

Iron Supplements and Foods Fortified With Iron
Concomitant administration of cefdinir with a therapeutic iron supplement containing 60 mg of elemental iron (as FeSO4) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during RANICEF 125 therapy, RANICEF 125 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. Therefore, RANICEF 125 for Oral Suspension can be administered with iron-fortified infant formula.
There have been reports of reddish stools in patients receiving cefdinir. In many cases, patients were also receiving iron-containing products. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

4.6 Pregnancy and Lactation: Pregnancy
Teratogenic Effects
Pregnancy Category B
Cefdinir was not teratogenic in rats 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) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on mg/m2/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

4.7 Effects on the ability to drive and use machines:
Not observed.

4.8 Undesirable effects:
Clinical Trials - (Pediatric Patients):
In clinical trials, 2289 pediatric patients (1783 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Forty of 2289 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for

gastrointestinal disturbances, usually diarrhea. Five of 2289 (0.2%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (N=1783 cefdinir- treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR SUSPENSION U.S. TRIALS IN PEDIATRIC PATIENTS (N=1783)[a]		
Incidence ≥1%	Diarrhea	8%
	Rash	3%
	Vomiting	1%
Incidence <1% but >0.1%	Cutaneous moniliasis	0.9%
	Abdominal pain	0.8%
	Leukopenia b	0.3%
	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 OBS ERVED WITH CEFDINIR SUSPENSION U.S. TRIALS IN PEDIATRIC PATIENTS (N=1783)		
Incidence ≥1%	↑Lymphocytes,↓Lymphocytes	2%, 0.8%
	↑Alkaline phosphatase	1%
	↓Bicarbonate [a]	1%
	↑Eosinophils	1%
	↑Lactate dehydrogenase	1%
	↑Platelets	1%
	↑PMNs, ↓PMNs	1%, 1%
	↑Urine protein	1%

Incidence <1% but >0.1%	↑Phosphorus, ↓Phosphorus	0.9%, 0.4%
	↑Urine pH	0.8%
	↓White blood cells, ↑White blood cells	0.7%, 0.3%
	↓Calcium [a]	0.5%
	↓Hemoglobin	0.5%
	↑Urine leukocytes	0.5%
	↑Monocytes	0.4%
	↑AST	0.3%
	↑Potassium [a]	0.3%
	↑Urine specific gravity, ↓Urine specific gravity	0.3%, 0.1%
	↓Hematocrit [a]	0.2%

[a] N = 1387 for these parameters.

4.9 Overdose

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 β-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.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for Systemic use – Third generation cephalosporins.

ATC code: J01DD15

Mechanism of Action:
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, β-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

Mechanism of Resistance:
Resistance to cefdinir is primarily through hydrolysis by some β-lactamases, alteration of penicillin-binding proteins (PBPs) and decreased permeability. Cefdinir is inactive against most strains of Enterobacter spp., Pseudomonas spp., Enterococcus spp., penicillin-resistant streptococci, and methicillin-resistant staphylococci. β-lactamase negative, ampicillin-resistant (BLNAR) H. influenzae strains are typically non-susceptible to cefdinir.

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

Gram-Positive Bacteria:

Staphylococcus aureus (methicillin-susceptible strains only)Streptococcus pneumoniae (penicillin-susceptible strains only) Streptococcus pyogenes
Gram-Negative Bacteria:
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

The following in vitro data are available, but their clinical significance is unknown.

Cefdinir exhibits in vitro minimum inhibitory concentrations (MICs) of 1 mcg/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.

Gram-Positive Bacteria:
Staphylococcus epidermidis (methicillin -susceptible strains only)
Streptococcus agalactiae
Viridans group streptococci
Gram-Negative Bacteria:
Citrobacter koseri Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

5.2 Pharmacokinetic properties

Absorption
Oral Bioavailability
Maximal plasma cefdinir concentrations occur 2 to 4 hours postdose following capsule or suspension 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). Following administration of suspension to healthy adults, cefdinir bioavailability is 120% relative to capsules. Estimated bioavailability of cefdinir capsules is 21% following administration of a 300 mg capsule dose, and 16% following administration of a 600 mg capsule dose. Estimated absolute bioavailability of cefdinir suspension is 25%. Cefdinir oral suspension of 250 mg/5 mL strength was shown to be bioequivalent to the 125 mg/5 mL strength in healthy adults under fasting conditions.

Effect of Food
The Cmax and AUC of cefdinir from the capsules are reduced by 16% and 10%, respectively, when given with a high-fat meal. In adults given the 250 mg/5 mL oral suspension with a high- fat meal, the Cmax and AUC of cefdinir are reduced by 44% and 33%, respectively. The magnitude of these reductions is not likely to be clinically significant because the safety and efficacy studies of oral suspension in pediatric patients were conducted without regard to food intake. Therefore, cefdinir may be taken without regard to food.

Cefdinir Suspension

Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 7- and 14-mg/kg oral doses of cefdinir to pediatric subjects (age 6 months-12 years) are presented in the following table:

Mean (± SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Suspension to Pediatric Subjects

Dose	C_{max} (µg/mL)	t_{max} (hr)	AUC (µg•hr/mL)
7 mg/kg	2.30 (0.65)	2.2 (0.6)	8.31 (2.50)
14 mg/kg	3.86 (0.62)	1.8 (0.4)	13.4 (2.64)

Multiple Dosing
Cefdinir does not accumulate in plasma following once- or twice-daily administration to subjects with normal renal function.

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.

Skin Blister
In adult subjects, median (range) maximal blister fluid cefdinir concentrations of 0.65 (0.33-1.1) and 1.1 (0.49-1.9) µg/mL were observed 4 to 5 hours following administration of 300- and 600-mg doses, respectively. Mean (± SD) blister Cmax and AUC (0-∞) values were 48% (± 13) and 91% (± 18) of corresponding plasma values.

Tonsil Tissue
In adult patients undergoing elective tonsillectomy, respective median tonsil tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.25 (0.22-0.46) and 0.36 (0.22-0.80) µg/g. Mean tonsil tissue concentrations were 24% (± 8) of corresponding plasma concentrations.

Sinus Tissue
In adult patients undergoing elective maxillary and ethmoid sinus surgery, respective median sinus tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were < 0.12 (< 0.12-0.46) and 0.21 (< 0.12-2.0) µg/g. Mean sinus tissue concentrations were 16% (± 20) of corresponding plasma concentrations.

Lung Tissue
In adult patients undergoing diagnostic bronchoscopy, respective median bronchial mucosa cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.78 (< 0.06-1.33) and 1.14 (< 0.06-1.92) µg/mL, and were 31% (± 18) of corresponding plasma concentrations. Respective median epithelial lining fluid concentrations were 0.29 (< 0.3-4.73) and 0.49 (< 0.3-0.59) µg/mL, and were 35% (± 83) of corresponding plasma concentrations.

Middle Ear Fluid
In 14 pediatric patients with acute bacterial otitis media, respective median middle ear fluid cefdinir concentrations 3 hours after administration of single 7- and 14-mg/kg doses were 0.21 (< 0.09-0.94) and 0.72 (0.14-1.42) µg/mL. Mean middle ear fluid concentrations were 15% (± 15) of corresponding plasma concentrations.

CSF
Data on cefdinir penetration into human cerebrospinal fluid are not available.

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 (t½) 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- 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

Patients with Renal Insufficiency
Cefdinir pharmacokinetics were investigated in 21 adult subjects with varying degrees of renal function. 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 t½ increased by approximately 2-fold and AUC by approximately 3-fold. In subjects with CLcr < 30 mL/min, Cmax increased by approximately 2-fold, t½ by approximately 5-fold, and AUC by approximately 6-fold. Dosage adjustment is recommended in patients with markedly compromised renal function.

Hemodialysis
Cefdinir pharmacokinetics were studied in 8 adult subjects undergoing hemodialysis. Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination t½ 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
The effect of age on cefdinir pharmacokinetics after a single 300-mg dose was evaluated in 32 subjects 19 to 91 years of age. Systemic exposure to cefdinir was substantially increased in older subjects (N = 16), 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 t½ 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.