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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS
RANICEF 300 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Ranicef 300 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains Cefdinir 300mg
See section 6.1 for full list of excipients

3. PHARMACEUTICAL FORM:

Film coated tablet

4. Clinical Particulars:

4.1 Therapeutic Indications:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RANICEF 300 and other antibacterial drugs, RANICEF 300 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 300 (cefdinir) capsules and RANICEF 300 (cefdinir) 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.

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:
For the treatment of acute bacterial otitis media. Oral dosage (oral suspension)
Infants and Children 6 months and older 7 mg/Icgtdose PO every 12 hours (Max: 300 mg/dose) for 5 to 10 days or 14 mg/kg/dose PO every 24 hours (Max: 600 mg/dose) for 10 days. Cefdinir is recommended by the American Academy of Pediatrics (AAP) as an alternative treatment to high-dose amoxicillin or high-dose amoxicillin: clavulanate. AAP recommends a 10-day course for any child with severe disease and for all patients younger than 2 years of age. regardless of severity. For children 2 to 5 years with mild to moderate disease. a 7-day course is acceptable.
For children at least 6 years old with mild to moderate disease. 5 to 7 days is acceptable.
Infants 2 to S months 7 mg/kg/dose PO every 12 hours or 14 1141g/dose PO every 24 hours for 10 days was recommended in previous clinical practice guidelines. In general. cefdinir is recommended by the AAP as an alternative treatment to amoxicillin for penicillin-allergic patients.
For the treatment of acute exacerbations of chronic bronchitis. Oral dosage (capsules) Adults and Adolescents 300 mg PO every 12 hours for 5 to 10 days or 600 mg PO every 24 hours for 10 days.
For the treatment of acute maxillaty sinusitis. Oral dosage Adults and Adolescents 300 ing PO every 12 hours or 600 mg PO every 24 hours for 10 days. Third-generation oral cephalosporins. such as cefdinir, are not recommended by the Infectious Disease Society of America (IDSA) for empiric monotherapy of acute bacterial sinusitis due to variable rates of S. pneumoniae resistance.
Infants >= 6 months and Children 7 mg/kg/dose PO every 12 hours (Max: 300 mg/dose) or 14 mg/kg/dose PO every 24 hours (Max: 600 mg/dose) for 10 days is recommended by the manufacturer. Third-generation oral cepludosporins, such as cefdinir. are not recommended by the Infectious Disease Society of America (IDSA) for empiric monotherapy of acute bacterial sinusitis due to variable rates of S. pneumoniae resistance.
For the treatment of community-acquired pneumonia. Oral dosage Adults 300 mg PO every 12 hours for 10 days. Cefdinir is suggested as an alternative in patients with penicillin-susceptible S. pneumoniae.
Adolescents 300 mg PO everyll hours for 10 days. Infants older than 3 months and Children
Cefdinir is recommended as an alternative to amoxicillin or amoxicillin; clavulanate in children with community-acquired pneumonia due to Haemophilus influenzae. Doses of 7 m2 kg/dose PO every 12 hours (Max: 300 mg/dose) are used for other indications and would be a reasonable dosage regimen. In general. treatment courses of 10 days have been the best-studied for CAP.
For the treatment of pharyngitis or tonsillitis. Oral dosage Adults and Adolescents

300 mg PO every 12 hours for 5 to 10 days or 600 mg PO every 24 hours for 10 days. The American Heart Association (AHA) does not recommended cefdinir for routine therapy for Group A Streptococcal pharyngitis therapy to prevent rheumatic fever. More narrow-spectrum cephalosporins (e.g.. cephalexin or cefadroxil) are preferred. In patients with no penicillin allergy. penicillin V or amoxicillin are the recommended agents.
Oral dosage (oral suspension) Infants and Children 6 months and older 7 mg/kg/dose PO every 12 hours (Max: 300 mg/dose) for 5 to 10 days or 14 mg/kg/dose PC) every 24 hours (Max: 600 mg/dose) for 10 days. The American Heart Association (AHA) does not recommended cefdinir for routine therapy for Group A Streptococcal pharyngitis therapy to prevent rheumatic fever. More narrow-spectrum cephalosporins (e.g., cephalexin or cefadroxil) are preferred. In patients with no penicillin allergy, penicillin V or amoxicillin are the recommended agents.
For the treatment of uncomplicated skin and skin structure infections. Oral dosage Adults and Adolescents 300 mg PO every 12 hours for 10 days. Oral dosage (oral suspension) Infants and Children 6 months and older 7 mg/kg/dose PO every 12 hours (Max: 300 mg/dose) for 10 days.
For the treatment of urinary tract infection (UTI) Oral dosage Adults 300 mg PO every 12 hours for 10 days. A 3- to 7-day course of cefidinir may be an alternative in patients with uncomplicated cystitis when other recommended agents cannot be used. Cefdinir has been shown to be statistically equivalent to cefaclor for microbiologic response rates and clinical cure rates in adults with uncomplicated urinary tract infection (UT!). Additionally. in a retrospective in vitro
antimicrobial susceptibility study (n = 456 urine samples from 30 medical sites). cefdinir was comparable or superior to other oral beta-lactams (i.e.. cefpodoxime. cefprozil. cefuroxime. clavulanate) for the treatment of UTI.
Infants, Children, and Adolescents 7 mg/kg/dose PO every 12 hours or 14 mg/kg/dose PO every 24 hours. A treatment course of 7 to 14 days is recommended by the American Academy of Pediatrics (AAP) for the treatment of initial UTI in febrile infants and young children 2 to 24 months of age. Shorter courses (2 to 4 days) may be used in older children with uncomplicated cystitis. In a retrospective in vitro antimicrobial susceptibility study in children. 95.6% of isolates (n = 412 of 431) recovered from the urine were susceptible to cefdinir. This rate was comparable or superior to rates for other antibiotics (i.e.. ampicillin. nitrofiwantoin: trimethoprim; sulfamethoxazole).

4.3 Contraindications:
RANICEF 300 (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 300 (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 300, 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 300 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 300 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 300 should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When RANICEF 300 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 300 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 300 therapy, RANICEF 300 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 300 therapy, RANICEF 300 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 300 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 300 therapy, RANICEF 300 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 300 therapy, RANICEF 300 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 300 tablet 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 1mg/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	1.8	13.4

	(0.62)	(0.4)	(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.

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.

5.3 Pre-clinical Safety:
Not available.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Sodium Lauryl Sulphate	BP
Microcrystalline Cellulose PH 101	BP
Croscarmellose Sodium	BP
PVPK-30	BP
Isopropyl Alcohol	BP
Magnesium Stearate	BP
Hypromellose	BP
Diethyl Phthalate	BP
Dichloromethane	BP
Titanium Dioxide	BP
Purified Talc	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: 24 months

6.4 Special Precautions for storage:
Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container:
Alu-Alu blister of 10 tablets packed in a Primary Carton along with the Pack insert.

6.6 Special precautions for disposal and other handling
No special requirements.

7. APPLICANT
FIDSON HEALTHCARE PLC
268 IKORODU ROAD, OBANIKORO, LAGOS STATE, NIGERIA

MANUFACTURER
Sterile-Gene Life Sciences Pvt Ltd
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