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SUMMARY OF SAFETY AND EFFECTIVENESS

SUBMITTED BY:

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NAME OF DEVICE:

Trade Name:	Ceftibuten, 30 mcg, Sensi-Discs Catalog Numbers 4331701, 4331702
Common Name/Description:	Antimicrobial Susceptibility Test Discs
Classification Name:	Antimicrobial Susceptibility Test Discs
PREDICATE DEVICE:	Other BBL® Sensi-Discs® such as Cefixime, 5 mcg, Sensi-Disc®

DEVICE DESCRIPTION:

INTENDED USE:

Antimicrobial Susceptibility Test Discs are used for semi-quantitative in vitro susceptibility testing by standardized agar diffusion test procedures. Ceftibuten Sensi-Discs® are intended for use in determining the susceptibility of gram-positive and gram-negative bacteria, including *Streptococcus peuemoniae* (penicillin-susceptible strains only), *Streptococcus pyrogens*, *Haemophilus influenzae,* (including β-lactamase-producing strains) and *Moraxella catarrhalis* (including β-lactamase-producing strains) species to Ceftibuten. Zone sizes used for interpretation of tests, including control organism limits, were determined by the antimicrobic manufacturer, Schering Corporation, and received FDA approval under NDA Nos. 50-685 and 50-686.

INDICATIONS FOR USE:

Use of BBL® Ceftibuten Sensi-Discs® for *in vitro* agar diffusion susceptibility testing is indicated when there is a need to determine the susceptibility of bacteria to Ceftibuten.

PRODUCT DESCRIPTION:

Ceftibuten Susceptibility Test Discs are prepared by impregnating high quality paper with accurately determined amounts of Ceftibuten supplied by the manufacturer, Schering Corporation, Kenilworth, New Jersey. Each Ceftibuten disc is clearly marked on both sides with the agent and content. Ceftibuten discs are furnished in cartridges of 50 discs each. Ceftibuten cartridges are packed as either a single cartridge in a single box, or in a package containing ten cartridges.

Agar diffusion methods employing dried filter paper discs impregnated with specific concentrations of antimicrobial agents were developed in the 1940s. In order to eliminate or minimize variability in the testing, Bauer et al. developed a standardized procedure in which Mueller Hinton Agar was selected as the test medium.

Various regulatory agencies and standards-writing organizations subsequently published standardized reference procedures based on the Bauer-Kirby method. Among the earliest and most widely accepted of these standardized procedures were those published by the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO). The procedure was adopted as a consensus standard by the National Committee for Clinical Laboratory Standards (NCCLS) and is periodically updated. The latest NCCLS documents are M2-A5 (12/93) and M100-S6 (12/95).

Discs containing a wide variety of antimicrobial agents are applied to the surface of Mueller Hinton Agar plates [or Haemophilus Test Medium Agar for *H. influenzae* or Mueller Hinton Agar with 5% Sheep Blood for *S. pneumoniae*] inoculated with pure cultures of clinical isolates. Following incubation, the plates are examined and the zones of inhibition surrounding the discs are measured and compared with established zone size ranges for individual antimicrobial agents in order to determine the agent(s) most suitable for use in antimicrobial therapy. The determination as to whether the organism in question is susceptible (S), intermediate (I), or resistant (R) to an antimicrobial agent is made by comparing zone sizes to those found in the respective organism tables

of National Committee for Clinical Laboratory Standards (NCCLS) Document M2-A5 ("Performance Standards for Antimicrobial Disk Susceptibility tests - Fifth Edition, Approved Standard", 12/93) and of NCCLS Document M100-S6 ("Performance Standards for Antimicrobial Susceptibility Testing", Sixth Informational Supplement, 12/95).

PERFORMANCE DATA:

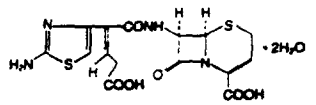
See attached Schering Corporation product insert section on Susceptibility testing Diffusion Techniques for CEDAX® (Ceftibuten).

CEDAX®
(ceftibuten capsules)
and
(ceftibuten for oral suspension)
FOR ORAL USE ONLY

DESCRIPTION:

CEDAX (ceftibuten capsules) and (ceftibuten for oral suspension) contain the active ingredient ceftibuten as ceftibuten dihydrate. Ceftibuten dihydrate is a semisynthetic cephalosporin antibiotic for oral administration. Chemically, it is (+)-(6R,7R)-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate. Its molecular formula is $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$. Its molecular weight is 446.43 as the dihydrate.

Ceftibuten dihydrate has the following structural formula:



CEDAX Capsules contain ceftibuten dihydrate equivalent to 400 mg of ceftibuten. Inactive ingredients contained in the capsule formulation include: magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell and/or band contains gelatin, sodium lauryl sulfate, titanium dioxide, and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butylparaben, propylparaben, and methylparaben.

CEDAX Oral Suspension after reconstitution contains ceftibuten dihydrate equivalent to either 90 mg of ceftibuten per 5 mL or 180 mg of ceftibuten per 5 mL. CEDAX Oral Suspension is cherry flavored and contains the inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1 g/5 mL), titanium dioxide, and xanthan gum.

CLINICAL PHARMACOLOGY:

PHARMACOKINETICS

Absorption:

CEDAX CAPSULES

Ceftibuten is rapidly absorbed after oral administration of CEDAX Capsules. The plasma concentrations and pharmacokinetic parameters of ceftibuten after a single 400-mg dose of CEDAX Capsules to 12 healthy adult male volunteers (20 to 39 years of age) are displayed in the table below. When CEDAX Capsules were administered once daily for 7 days, the average C_{max} was 17.9 μg/mL on day 7. Therefore, ceftibuten accumulation in plasma is about 20% at steady state.

CEDAX ORAL SUSPENSION

Ceftibuten is rapidly absorbed after oral administration of CEDAX Oral Suspension. The plasma concentrations and pharmacokinetic parameters of ceftibuten after a single 9-mg/kg dose of CEDAX Oral Suspension to 32 fasting pediatric patients (6 months to 12 years of age) are displayed in the following table:

Parameter	Average Plasma Concentration (in μg/mL of ceftibuten after a single 400-mg dose) and Derived Pharmacokinetic Parameters (± 1 SD) (n = 12 healthy adult males)	Average Plasma Concentration (in μg/mL of ceftibuten after a single 9-mg/kg dose) and Derived Pharmacokinetic Parameters (± 1 SD) (n = 32 pediatric patients)
1.0 h	6.1 (5.1)	9.3 (6.3)
1.5 h	9.9 (5.9)	8.6 (4.4)
2.0 h	11.3 (5.2)	11.2 (4.6)
3.0 h	13.3 (3.0)	9.0 (3.4)
4.0 h	11.2 (2.9)	6.6 (3.1)
6.0 h	5.8 (1.8)	3.8 (2.5)
8.0 h	3.2 (1.0)	1.6 (1.3)
12.0 h	1.1 (0.4)	0.5 (0.4)
C_{max}, μg/mL	15.0 (3.3)	13.4 (4.9)
T_{max}, h	2.6 (0.9)	2.0 (1.0)
AUC, μg•h/mL	73.7 (16.0)	56.0 (16.9)
$T_{1/2}$, h	2.4 (0.2)	2.0 (0.6)
Total body clearance (Cl/F) mL/min/kg	1.3 (0.3)	2.9 (0.7)

The absolute bioavailability of CEDAX Oral Suspension has not been determined. The plasma concentrations of ceftibuten in pediatric patients are dose proportional following single doses of CEDAX Capsules of 200 mg and 400 mg and of CEDAX Oral Suspension between 4.5 mg/kg and 9 mg/kg.

Distribution:

CEDAX CAPSULES

The average apparent volume of distribution (V/F) of ceftibuten in 6 adult subjects is 0.21 L/kg (± 1 SD = 0.03 L/kg).

CEDAX ORAL SUSPENSION

The average apparent volume of distribution (V/F) of ceftibuten in 32 fasting pediatric patients is 0.5 L/kg (± 1 SD = 0.2 L/kg).

Protein Binding:

Ceftibuten is 65% bound to plasma proteins. The protein binding is independent of plasma ceftibuten concentration.

Tissue Penetration:

Bronchial secretions: In a study of 15 adults administered a single 400-mg dose of ceftibuten and scheduled to undergo bronchoscopy, the mean concentrations in epithelial lining fluid and bronchial mucosa were 15% and 37%, respectively, of the plasma concentrations.

Sputum: Ceftibuten sputum levels average approximately 7% of the concomitant plasma ceftibuten level. In a study of 24 adults administered ceftibuten 200 mg bid or 400 mg qd, the average C_{max} in sputum (1.5 μg/mL) occurred at 2 hours postdose and the average C_{max} in plasma (17 μg/mL) occurred at 2 hours postdose.

Middle-ear fluid (MEF): Ceftibuten middle-ear fluid levels average approximately 50% of the concomitant plasma ceftibuten level. In a study of 30 children administered 9 mg/kg of ceftibuten, the average C_{max} in MEF (2.9 ± 0.9 μg/mL) occurred at 4 hours postdose and the average C_{max} in plasma (6.7 ± 1.9 μg/mL) occurred at 2 hours postdose.

Tonsillar tissue: Data on ceftibuten penetration into tonsillar tissue are not available.

Cerebrospinal fluid: Data on ceftibuten penetration into cerebrospinal fluid are not available.

Metabolism and Excretion:

A study with radiolabeled ceftibuten administered to 6 healthy adult male volunteers demonstrated that *cis*-ceftibuten is the predominant component in both plasma and urine. About 10% of ceftibuten is converted to the *trans*-isomer. The *trans*-isomer is approximately ¼ as antimicrobially potent as the *cis*-isomer.

Ceftibuten is excreted in the urine: 95% of the administered radioactivity was recovered either in urine or feces. In 6 healthy adult male volunteers, approximately 56% of the administered dose of ceftibuten was recovered in the feces within 24 hours. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment (see **DOSAGE AND ADMINISTRATION**).

Food Effect on Absorption:

Food affects the bioavailability of ceftibuten from CEDAX Capsules and CEDAX Oral Suspension.

The effect of food on the bioavailability of CEDAX Capsules was evaluated in 26 healthy adult male volunteers who ingested 400 mg of CEDAX Capsules after an overnight fast or immediately after a standardized breakfast. Results showed that food delays the time of C_{max} by 1.75 hours, decreases the C_{max} by 18%, and decreases the extent of absorption (AUC) by 8%.

The effect of food on the bioavailability of CEDAX Oral Suspension was evaluated in 18 healthy adult male volunteers who ingested 400 mg of CEDAX Oral Suspension after an overnight fast or immediately after a standardized breakfast. Results obtained demonstrated a decrease in C_{max} of 26% and an AUC of 17% when CEDAX Oral Suspension was administered with a high-fat breakfast, and a decrease in C_{max} of 17% and in AUC of 12% when CEDAX Oral Suspension was administered with a low-calorie nonfat breakfast (see **PRECAUTIONS**).

Bioequivalence of Dosage Formulations:

A study in 18 healthy adult male volunteers demonstrated that a 400-mg dose of CEDAX Capsules produced equivalent concentrations to a 400-mg dose of CEDAX Oral Suspension. Average C_{max} values were 15.6 (3.1) μg/mL for the capsule and 17.0 (3.2) μg/mL for the suspension. Average AUC values were 80.1 (14.4) μg•hr/mL for the capsule and 87.0 (12.2) μg•hr/mL for the suspension.

Special Populations:

Geriatric patients: Ceftibuten pharmacokinetics have been investigated in elderly (65 years of age and older) men (n = 8) and women (n = 4). Each volunteer received ceftibuten 200-mg capsules twice daily for 3½ days. The average C_{max} was 17.5 (3.7) μg/mL after 3½ days of dosing compared to 12.9 (2.1) μg/mL after the first dose; ceftibuten accumulation in plasma was 40% at steady state. Information regarding the renal function of these volunteers was not available; therefore, the significance of this finding for clinical use of CEDAX Capsules in elderly patients is not clear. Ceftibuten dosage adjustment in elderly patients may be necessary (see **DOSAGE AND ADMINISTRATION**).

Patients with renal insufficiency: Ceftibuten pharmacokinetics have been investigated in adult patients with renal dysfunction. The ceftibuten plasma half-life increased and apparent total clearance (Cl/F) decreased proportionately with increasing degree of renal dysfunction. In 6 patients with moderate renal dysfunction (creatinine clearance 30 to 49 mL/min), the plasma half-life of ceftibuten increased to 7.1 hours and Cl/F decreased to 30 mL/min. In 6 patients with severe renal dysfunction (creatinine clearance 5 to 29 mL/min), the half-life increased to 13.4 hours and Cl/F decreased to 16 mL/min. In 6 functionally anephric patients (creatinine clearance <5 mL/min), the half-life increased to 22.3 hours and Cl/F decreased to 11 mL/min (a 7- to 8-fold change compared to healthy volunteers). Hemodialysis removed 65% of the drug from the blood in 2 to 4 hours. These changes serve as the basis for dosage adjustment recommendations in adult patients with mild to severe renal dysfunction (see **DOSAGE AND ADMINISTRATION**).

Microbiology:

Ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall. This binding leads to inhibition of cell-wall synthesis.

Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.* Like other beta-lactam agents, ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes like penicillin-resistant *S. pneumoniae.*

Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**):

Gram-positive aerobes:

Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Gram-negative aerobes:

Haemophilus influenzae (including β-lactamase-producing strains)
Moraxella catarrhalis (including β-lactamase-producing strains)

There are no known organisms which are potential pathogens in the indications approved for ceftibuten for which ceftibuten exhibits *in vitro* activity but for which the safety and efficacy of ceftibuten in treating clinical infections due to these organisms, have not been established in adequate and well-controlled trials.

NOTE: Ceftibuten is INACTIVE *in vitro* against *Acinetobacter, Bordetella, Campylobacter, Enterobacter, Enterococcus, Flavobacterium, Hafnia, Listeria, Pseudomonas, Staphylococcus,* and *Streptococcus* (except *pneumoniae* and *pyogenes*) species. In addition, it shows little *in vitro* activity against most anaerobes, including most species of *Bacteroides.*

Susceptibility Testing:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth, agar, or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftibuten powder. The MIC values should be interpreted according to the following criteria when testing *Haemophilus* species using Haemophilus Test Media (HTM):

MIC (μg/mL)	Interpretation
≤2	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated.

Ceftibuten is indicated for penicillin-susceptible only strains of *Streptococcus pneumoniae.* A pneumococcal isolate that is susceptible to penicillin (MIC ≤0.06 μg/mL) can be considered susceptible to ceftibuten for approved indications. Testing of ceftibuten against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for ceftibuten are not currently available. Physicians should be informed that clinical response rates with ceftibuten may be lower in strains that are not penicillin-susceptible.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspect of laboratory procedures. Standard ceftibuten powder should provide the following MIC values:

Organism	MIC range (μg/mL)
Haemophilus influenzae ATCC 49274	0.25-1.0

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of ceftibuten to test the susceptibility of microorganisms to ceftibuten.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-μg ceftibuten disk should be interpreted according to the following criteria when testing *Haemophilus* species using Haemophilus Test Media (HTM):

Zone diameter (mm)	Interpretation
≥28	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques.

Ceftibuten is indicated for penicillin-susceptible only strains of *Streptococcus pneumoniae.*

Pneumococcal isolates with oxacillin zone sizes of ≥20 mm are susceptible to penicillin and can be considered susceptible for approved indications. Reliable disk diffusion tests for cefdituren do not yet exist.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg cefdituren disk should provide the following zone diameters in these laboratory test quality control strains:

Organism	Zone diameter (mm)
Haemophilus influenzae ATCC 49247	29-35

Cephalosporin-class disks should not be used to test for susceptibility to cefdituren.

INDICATIONS AND USAGE:

CEDAX (cefdituren) is indicated for the treatment of individuals with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below (see **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES** sections).

Acute Bacterial Exacerbations of Chronic Bronchitis due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only).

NOTE: In acute bacterial exacerbations of chronic bronchitis clinical trials where Moraxella catarrhalis was isolated from infected sputum at baseline, cefdituren clinical efficacy was 22% less than control.

Acute Bacterial Otitis Media due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pyogenes*.

NOTE: Although cefdituren used empirically was equivalent to comparators in the treatment of clinically and/or microbiologically documented acute otitis media, the efficacy against *Streptococcus pneumoniae* was 23% less than control. Therefore, cefdituren should be given empirically only when adequate antimicrobial coverage against *Streptococcus pneumoniae* has been previously administered.

Pharyngitis and Tonsillitis due to *Streptococcus pyogenes*.

NOTE: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefdituren is generally effective in the eradication of *Streptococcus pyogenes* from the oropharynx however, data establishing the efficacy of CEDAX for the prophylaxis of subsequent rheumatic fever are not available.

CONTRAINDICATIONS:

CEDAX (cefdituren) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS:

BEFORE THERAPY WITH CEDAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEDAX, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEDAX OCCURS, DISCONTINUE THE DRUG. 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 cefdituren, 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.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

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 measures should be taken.

The dose of cefdituren may require adjustment in patients with varying degrees of renal insufficiency, particularly in patients with creatinine clearance less than 50 mL/min or undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION**). Cefdituren is readily dialyzable. Dialysis patients should be monitored carefully, and administration of cefdituren should occur immediately following dialysis.

Cefdituren should be prescribed with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Information to Patients:

Patients should be informed that:

- If the patient is diabetic, he/she should be informed that CEDAX Oral Suspension contains 1 gram sucrose per teaspoon of suspension.
- CEDAX Oral Suspension should be taken at least 2 hours before a meal or at least 1 hour after a meal (see **CLINICAL PHARMACOLOGY, Food Effect on Absorption**).

Drug Interactions:

Theophylline: Twelve healthy male volunteers were administered one 200-mg cefdituren capsule twice daily for 6 days. With the morning dose of cefdituren on day 6, each volunteer received a single intravenous infusion of theophylline (4 mg/kg). The pharmacokinetics of theophylline were not altered. The effect of cefdituren on the pharmacokinetics of theophylline administered orally has not been investigated.

Antacids or H_2-receptor antagonists: The effect of increased gastric pH on the bioavailability of cefdituren was evaluated in 18 healthy adult volunteers. Each volunteer was administered one 400-mg cefdituren capsule. A single dose of liquid antacid did not affect the C_{max} or AUC of cefdituren; however, 150 mg of ranitidine q12h for 3 days increased the cefdituren C_{max} by 23% and cefdituren AUC by 16%. The clinical relevance of these increases is not known.

Drug/Laboratory Test Interactions:

There have been no chemical or laboratory test interactions with cefdituren noted to date. False-positive direct Coombs' tests have been reported during treatment with other cephalosporins. Therefore, it should be recognized that a positive Coombs' test could be due to the drug. The results of assays using red cells from healthy subjects to determine whether cefdituren would cause direct Coombs reactions *in vitro* showed no positive reaction at cefdituren concentrations as high as 40 µg/mL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term animal studies have not been performed to evaluate the carcinogenic potential of cefdituren. No mutagenic effects were seen in the following studies: *in vitro* chromosome assay in human lymphocytes, *in vivo* chromosome assay in mouse bone marrow cells, Chinese Hamster Ovary (CHO) cell point mutation assay at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus, and in a bacterial reversion point mutation test (Ames). No impairment of fertility occurred when rats were administered cefdituren orally up to 2000 mg/kg/day (approximately 43 times the human dose based on mg/m²/day).

Pregnancy: Teratogenic effects: Pregnancy Category B:

Cefdituren was not teratogenic in the pregnant rat at oral doses up to 400 mg/kg/day (approximately 8.6 times the human dose based on mg/m²/day). Cefdituren was not teratogenic in the pregnant rabbit at oral doses up to 40 mg/kg/day (approximately 1.5 times the human dose based on mg/m²/day) and has revealed no evidence of harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

Cefdituren has not been studied for use during labor and delivery. Its use during such clinical situations should be weighed in terms of potential risk and benefit to both mother and fetus.

Nursing Mothers:

It is not known whether cefdituren (at recommended dosages) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cefdituren is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of cefdituren in infants less than 6 months of age has not been established.

Geriatric Patients:

The usual adult dosage recommendation may be followed for patients in this age group. However, these patients should be monitored closely, particularly their renal function, as dosage adjustment may be required.

ADVERSE EVENTS:

Clinical Trials:

CEDAX CAPSULES (adult patients)

In clinical trials, 1728 adult patients (1092 US and 636 international) were treated with the recommended dose of cefdituren capsules (400 mg per day). There were no deaths or permanent disabilities thought due to drug toxicity in any of the patients in these studies. Thirty-six of 1728 (2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea, vomiting, or nausea. Six of 1728 (0.3%) patients were discontinued due to rash or pruritus thought related to cefdituren administration.

In the US trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefdituren capsules in multiple-dose clinical trials (*n* = 1092 cefdituren-treated patients).

ADVERSE REACTIONS CEFTIBUTEN CAPSULES US CLINICAL TRIALS IN ADULT PATIENTS (n = 1092)		
Incidence equal to or greater than 1%	Nausea	4%
	Headache	3%
	Diarrhea	3%
	Dyspepsia	2%
	Dizziness	1%
	Abdominal pain	1%
	Vomiting	1%
Incidence less than 1% but greater than 0.1%	Anorexia	
	Constipation	
	Dry mouth	
	Dyspnea	
	Dysuria	
	Eructation	
	Fatigue	
	Flatulence	
	Loose stools	
	Moniliasis	
	Nasal congestion	
	Paresthesia	
	Pruritus	
	Rash	
	Somnolence	
	Taste perversion	
	Urticaria	
	Vaginitis	

LABORATORY VALUE CHANGES* CEFTIBUTEN CAPSULES US CLINICAL TRIALS IN ADULT PATIENTS		
Incidence equal to or greater than 1%	↑ BUN	4%
	↑ Eosinophils	3%
	↓ Hemoglobin	2%
	↑ ALT (SGPT)	1%
	↑ Bilirubin	1%
Incidence less than 1% but greater than 0.1%	↑ Alk phosphatase	
	↑ Creatinine	
	↑ Platelets	
	↓ Platelets	
	↓ Leukocytes	
	↑ AST (SGOT)	

*Changes in laboratory values with possible clinical significance regardless of whether or not the investigator thought that the change was due to drug toxicity.

CEDAX ORAL SUSPENSION (pediatric patients)

In clinical trials, 1152 pediatric patients (772 US and 380 international), 97% of whom were younger than 12 years of age, were treated with the recommended dose of cefdituren (9 mg/kg once daily up to a maximum dose of 400 mg per day) for 10 days. There were no deaths, life-threatening adverse events, or permanent disabilities in any of the patients in these studies. Eight of 1152 (<1%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily (7 out of 8) for gastrointestinal disturbances, usually diarrhea or vomiting. One patient was discontinued due to a cutaneous rash thought possibly related to cefdituren administration.

In the US trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefdituren oral suspension in multiple-dose clinical trials (*n* = 772 cefdituren-treated patients).

ADVERSE REACTIONS CEFTIBUTEN ORAL SUSPENSION US CLINICAL TRIALS IN PEDIATRIC PATIENTS (n = 772)		
Incidence equal to or greater than 1%	Diarrhea*	4%
	Vomiting	2%
	Abdominal pain	2%
	Loose stools	2%
Incidence less than 1% but greater than 0.1%	Agitation	
	Anorexia	
	Dehydration	
	Diaper dermatitis	
	Dizziness	
	Dyspepsia	
	Fever	
	Headache	
	Hematuria	
	Hyperkinesia	
	Insomnia	
	Irritability	
	Nausea	
	Pruritus	
	Rash	
	Rigors	
	Urticaria	

*NOTE: The incidence of diarrhea in children ≤2 years old was 8% (23/301) compared with 2% (9/471) in children >2 years old.