CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50749

MICROBIOLOGY REVIEW(S)

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Division of Anti-Infective Drug Products
Clinical Microbiological Review

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DRUG PRODUCT NAME

Proprietary:	Omnicef™ Capsules and Suspension
Nonproprietary/USAN:	Cefdinir capsules and suspension
Code Names/#'s:	CI-983, PD 134393, FK 482, BMY 28488, CAS-91832-40-5

PHARMACOLOGICAL CATEGORY:
Cephalosporin, for treatment of mild to moderate bacterial infections in an outpatient setting.

DOSAGE FORM: Capsules and Suspension

STRENGTHS: 300 mg/capsule
125 mg/5 mL suspension

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _X_ Rx ___ OTC

RELATED DOCUMENTS (if applicable):
IND/
DMFs:/

REMARKS/COMMENTS:

This application provides a proposal for the marketing of a semisynthetic cephalosporin, Cefdinir, for the treatment of patients with community acquired pneumonia, acute exacerbations of chronic bronchitis, acute otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 507(b) of the Act when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 127 to 134.

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS

I. INTRODUCTION

Cefdinir is a new, orally administered member of the cephalosporin class of β-lactam antimicrobial agents. It has been evaluated in clinical trials in adults and children against community-acquired infections of the upper and lower respiratory tracts and infections of the skin and skin structures. Due to its spectrum of antimicrobial activity and pattern of β-lactamase resistance, cefdinir was targeted against the following species of bacteria: *Staphylococcus aureus*, *Streptococcus agalactiae*, *S. pneumoniae*, *S. pyogenes*, *Escherichia coli*, *Haemophilus influenzae*, *H. parainfluenzae*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis*.

Based on pilot plasma concentration studies performed in humans, the recommended cefdinir regimen for the treatment of infections in adults, using a capsule formulation, is either 300 mg twice a day or 600 mg once daily. The equivalent oral doses of suspension in children, ranging in age from 6 months to 12 years, are 7 mg/kg twice a day or 14 mg/kg once daily.

II. PRECLINICAL EFFICACY (*IN VITRO*)

A. Mechanism of Action

Cephalosporins exert their antibacterial activity by inhibiting bacterial cell wall synthesis. β-lactams bind to proteins on the inner surface of the bacterial cell membrane. These proteins, penicillin binding proteins (PBPs), are of 3 classes: transpeptidases; carboxypeptidases; and endopeptidases. These enzymes are responsible for the final assembly of newly synthesized cell wall, external to the cell membrane.

Cephalosporins inhibit the transpeptidase enzyme responsible for cross-linking nascent peptidoglycan. The cephalosporin β-lactam ring sterically mimics the D-ala-D-ala amino acid sequence of the pentapeptide precursor, covalently binding at the transpeptidase active site, rendering the enzyme and the cephalosporin inactive. Cephalosporins are bactericidal by virtue of cell wall synthesis inhibition, although the actual killing mechanism is unclear.

In a study by Yasuhiro Mine et al.[1] relative PBPs affinities of cefdinir in *S. aureus* 209P JC-1, *E. faecalis* FP183, and *E. coli* NIHJ JC-2 were investigated. The data are presented in Table 1. Affinities of cefdinir for PBPs 1, 2, and 3 (classified by molecular weight) of *S. aureus* and PBPs 1a, 1bs, 2, 3, and 4 of *E. coli* were generally equal to or greater than those of cefixime, cefaclor, or cephalexin. Cefdinir and the 3 reference drugs had poor affinity for PBP 4 of *S. aureus* and PBPs 5 and 6 of *E. coli*. Against *E. faecalis* PBPs, cefdinir showed very high affinity for PBP 2 and 3, moderate affinity for PBP 1, and low affinity for PBPs 5 and 4, while cefaclor showed very high affinity for PBPs 2 and 1, moderate affinity for PBP 3, and low affinity for PBPs 4 and 5.

TABLE 1. Affinity of Cefdinir and Reference Antibiotics for Penicillin-Binding Proteins (PBPs)

	PBPs	IC_{50}[a]			
		Cefdinir	Cefixime	Cefaclor	Cephalexin
Staphylococcus aureus 209P JC-1	1	0.58	2.9	0.2	0.2
	2	0.17	<0.2	125	1.7
	3	0.12	6.2	<0.2	0.2
	4	28	25	>125	24
MIC (μg/mL)		0.20	25	0.78	1.56
Enterococcus faecalis FP183	1	7.9		0.66	
	2	<0.2		<0.2	
	3	<0.2		6.1	
	4	>125		26	
	5	74		97	
MIC (μg/mL)		12.5		100	
Escherichia coli NIHJ JC-2	1a	0.09	<0.2	1.6	0.8
	lbs	2.3	≤0.2	7.2	>125
	2	1.6	16	27	≥125
	3	0.07	0.2	1.6	8.7
	4	1.1	>125	1.6	3.0
	5	>125	>125	>25	>125
	6	>125	13	>25	>125
MIC (μg/mL)		0.2	0.2	3.13	12.5

[a] Inhibitory concentrations (μg/mL) of drug required to reduce [^{14}C]benzylpenicillin binding by 50%

Takeshi Yokota et al.[2] supported part of the above information by reporting that cefdinir manifested higher binding affinities to PBPs 2 and 3 of *S. aureus* 209P, PBP 1bs, 2, 3, and 4 of *E. coli* NIHJ JC-2, and all fractions except PBP 2B of *S. pneumoniae* 13 than cefaclor. Kazuo Hatano et al.[4] also demonstrated that cefdinir's high binding affinities for PBPs, 2, and 3 of *S. aureus* and PBPs 1 and 2 of *S. pyogenes* were the reason for drastic morphological changes and antibacterial activity.

Consistent with this mechanism of action, cefdinir induced filamentation in *E. coli* at concentrations as low as 0.025 μg/mL and produced lysis at 0.78 μg/mL.[3] Exposure of *E. faecalis* to 6.25 μg/mL of cefdinir for 2 hours produced nonseparating cells with a multiple thick

cross wall and 10% lysis.[5] In *S. aureus* exposed to cefdinir at concentrations as low as 0.05μg/mL, the cross walls were swollen, the next cross wall synthesis started before completion of septation, and lysis was triggered at the site of cross wall formation resulting in cell skeletons in most cells. In *S. pyogenes*, 0.012μg/mL of cefdinir induced swollen and incomplete cross walls, as well as lysis in a large cell population; and at 0.048 μg/mL, there was almost complete inhibition of cross wall formation and lysed cells.[4]

B. Antimicrobial Spectrum of Activity

Cefdinir has been tested for *in vitro* activity against a variety of microorganisms derived from infections throughout the world. The data derived from these studies are summarized in Table 2. These studies were conducted using standardized and controlled *in vitro* susceptibility test methods. Minimum inhibitory concentrations (MICs) were determined by a dilution method, most commonly using Mueller-Hinton (MH) broth for aerobes, supplemented as required for support of factitious organisms and Wilkins-Chalgren (WC) agar for anaerobes. For investigators using broth microdilution methods an inoculum of about 10^5 CFU per milliliter was used in most studies. For investigators using agar dilution an inoculum of about 10^4 CFU per spot for aerobes and 10^5 CFU per spot for anaerobes was used in most studies. Tests for aerobes were read after overnight incubation at 35-37°C, but some anaerobes required up to 48 hours incubation. These agar and inocula are those recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

The sponsor proposed susceptibility criteria based on human pharmacokinetics data[6] and the 600-mg once or 300-mg twice daily dose of cefdinir used in clinical evaluations, as follows: Susceptible, MIC≤1.0μg/mL; Intermediate, MIC = 2 μg/mL; and Resistant, MIC ≥4 μg/mL.

Using these criteria, most species of gram-positive isolates are susceptible (median MIC_{90}s ≤1.0 μg/mL) to cefdinir. This includes the following species: *Gardnerella vaginalis*; *Gemella morbillorum*; methicillin/oxacillin-susceptible isolates of *Staphylococcus aureus, S. epidermidis, S. haemolyticus, S. saprophyticus, S. xylosus*, and coagulase-negative Staphylococci; *S. capitis; S. cohnii; S. hominis, S. simulans; Streptococcus anginosus; S. bovis; S. constellatus; S. equinus; S. pyogenes; S. agalactiae; S. intermedius; S. mitis*; penicillin-susceptible *S. pneumoniae*; *S. salivarius*; and *S. sanguis.*

In addition, the following fastidious gram-negative bacteria are susceptible to cefdinir: *Haemophilus influenzae* and *H. parainfluenzae*; *Moraxella catarrhalis*; *Neisseria gonorrhoeae*, and *N. meningitidis*. Cefdinir's activity extends to *Aeromonas hydrophila* and the following enteric species: *Citrobacter diversus*; *Pantoea (Enterobacter) agglomerans* and *E. sakazakii*; *Escherichia coli; Klebsiella oxytoca* and *K. pneumoniae; Proteus mirabilis; Salmonella enteritidis* and *S. typhi*; and *Yersinia enterocolitica.*

Susceptible strictly anaerobic species are *Clostridium perfringens; Peptostreptococcus anaerobius, P. asaccharolyticus, P. magnus, P. micros,* and *P. prevotii; Porphyromonas gingivalis; Prevotella intermedia* and *P. oralis;* and *Propionibacterium acnes.*

According to the sponsor since spectrum of activity of cefdinir includes bacterial strains that produce a wide variety of ß-lactamases, cefdinir has been evaluated in clinical trials as an oral cephalosporin for the treatment of the following community-acquired infections:

Lower Respiratory Tract Infections:

- Community-acquired pneumonia caused by susceptible strains of *Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis, Escherichia coli,* and *Klebsiella pneumoniae.*

- Acute exacerbations of chronic bronchitis caused by susceptible strains of *Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis, Escherichia coli,* and *Klebsiella pneumoniae.*

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Upper Respiratory Tract Infections:

- [

- Acute maxillary sinusitis caused by susceptible strains of *Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, S. pyogenes, Staphylococcus aureus, Moraxella catarrhalis, Escherichia coli,* and *Klebsiella pneumoniae.*

- Pharyngitis/tonsillitis caused by susceptible strains of *Streptococcus pyogenes.*

Uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae,* and *Klebsiella pneumoniae.*

An analysis of the activity of cefdinir against the most frequently encountered pathogens is given in Table 3. Included for reference are other oral cephalosporins with similar antibacterial properties and the most commonly used oral penicillin (amoxicillin). The data show that cefdinir has good antibacterial activity against most of the bacterial strains isolated from the infections

described above, i.e., methicillin/oxacillin-susceptible *Staphylococcus aureus*; *Streptococcus pyogenes*; penicillin-susceptible *Streptococcus pneumoniae*; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Escherichia coli*; and *Klebsiella pneumoniae*. Cefdinir is almost 10-fold more active against methicillin/oxacillin-susceptible *Staphylococcus aureus* than cefpodoxime, the compound with the most similar spectrum. Cefdinir is also almost 10-fold more active against methicillin/oxacillin-susceptible *Staphylococcus aureus*; *Streptococcus pyogenes;* penicillin-susceptible *Streptococcus pneumoniae; Haemophilus influenzae; Moraxella catarrhalis; Escherichia coli*; and *Klebsiella pneumoniae* than the comparator cefaclor.

Cefdinir is not effective against all the Enterococci, methicillin/oxacillin-resistant staphylococci, penicillin-resistant pneumococci, all the *Acinetobacter* species, *Burkholderia cepacia*, all *legionella* species, all the pseudomonads, *Stenotrophomonas maltophilia*, all *Citrobacter* species, *Enterobacter aerogenes*, *E. Cloacae*, *Morganella morganii*,*Proteus vulgaris*, all *Providencia* species, and all *Serratia* species.

The NDA holders letter of January 1993 suggested that at least 100 isolates from each species should be tested. Therefore, only species with around 100 isolates will be considered for inclusion in the *in vitro* section (second list) of the package insert. The NDA holders letter also states that in order to be included in the label (second list) a microorganism should be a significant (not anecdotal) pathogen at the body site(s) or in the infection(s) for which clinical effectiveness for other pathogens has been established. Since the sponsor is requesting community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections, only potential pathogenic microorganisms usually found at these sites will be included in the second list of the label.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 1 of 7)

Organism	Median MIC_{90}	MIC_{90} Range	N°	MIC Range	References
Gram-Positive					
Bacillus cereus			3	4-50	7, 8
Corynebacterium jeikeium	>16	>16	10	0.06->16	7
Corynebacterium spp			5	≤0.025-128	8, 9
Enterococcus avium	>100	50->100	102	0.4->100	5, 10-13
E. faecium	>100	>64->128	275	0.1->128	2, 5, 10-17
E. faecalis	>16	1.6->128	1093	≤0.015->128	1, 2, 7, 10-31
Enterococcus spp	16	>4->128	413	0.25->128	7, 9, 21, 32-39
Gardnerella vaginalis	0.5	0.5	26	0.06-6.25	14, 40
Gemella morbillorum	0.4	0.4	10	0.05-0.4	8
G. haemolysans			1	≤0.025	8
Listeria monocytogenes	5.4	4-8	91	0.25-64	7, 14, 15, 24, 35
Staphylococcus aureus[b]	0.8	0.03->100	1865	≤0.002->128	2, 8, 10, 14, 15, 18, 21, 22, 25, 27-31, 33, 38, 39, 41-51
methicillin/oxacillin-resistant	>64	>16->128	925	0.2->128	1, 2, 7, 9-20, 23, 24, 31, 32, 35, 36, 41, 52, 53
methicillin/oxacillin-susceptible	0.5	0.1-12.5	1609	0.008-25	1, 2, 7, 9, 11-14, 16, 17, 19, 20, 23, 24, 32, 34-37, 41, 44, 52-55
Staphylococcus sp. coagulase-negative[b]	4	≤0.015->128	916	0.008->128	2, 7, 8, 15, 21, 29, 30, 33, 36, 44, 49

methicillin/oxacillin-resistant	>128	>64->256	141	≤0.03->256	9, 15, 16, 18, 24, 35, 52, 53
methicillin/oxacillin-susceptible	1	0.1-2	302	≤0.01-8	9, 16, 18, 24, 35, 37, 52, 53
S. capitis	0.5	0.5	11	0.1-64	54
S. cohnii	1	1	10	0.25-1	14
S. epidermidis[b]	4	≤0.06->128	526	≤0.025->128	1, 7, 8, 10-14, 21, 26-28, 32, 34, 38, 39, 41, 44, 49, 50
methicillin/oxacillin-resistant	>100	>64->128	89	0.03->128	14, 17, 20, 23
methicillin/oxacillin-susceptible	0.1	0.06-3.1	118	0.01-3.1	14, 17, 20, 23, 54

[a] Number of strains
[b] Methicillin/oxacillin susceptibility unspecified
[c] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 2 of 7)

Organism	Median MIC_{90}	MIC_{90} Range	N[a]	MIC Range	References[c]
Gram-Positive (cont)					
S. haemolyticus[b]	>64	>4->128	208	≤0.025->128	1, 8, 21, 41, 53
methicillin/oxacillin-resistant			7	16->128	14, 20
methicillin/oxacillin-susceptible	0.5	0.5-32	33	0.03->64	14, 20, 54
S. hominis[b]	0.1	0.1	17	0.03-0.4	1, 14
methicillin/oxacillin-susceptible	0.1	0.1	12	0.03-0.1	20, 54
S. saprophyticus[b]	2	0.25-4	267	0.008->128	1, 14, 17, 30, 41, 53, 56
methicillin/oxacillin-resistant			6	2-16	56
methicillin/oxacillin-susceptible	0.5	0.25-4	203	0.1->16	20, 54, 56
S. simulans[b]	0.1	0.1	23	≤0.025-2	8, 14, 56
methicillin/oxacillin-susceptible	1	1	32	0.1-2	20, 56
S. warneri			4	0.03-0.06	14
S. xylosus					
methicillin/oxacillin-susceptible	0.5	0.5	15	0.03-8	54
Staphylococcus spp[b]	1	1-64	69	0.06->128	21, 41, 56, 57
methicillin/oxacillin-resistant			5	2-16	56
methicillin/oxacillin-susceptible	2	2	31	0.03-16	56
Streptococcus anginosus	0.1	0.05-0.25	52	0.02-0.25	8, 14
S. bovis			1	≤0.03	7
S. constellatus	0.1	0.1	25	≤0.025-0.1	8
S. equinus			2	0.2	8
S. Group A *(pyogenes)*	≤0.03	0.008-0.1	1204	≤0.002-6	1, 2, 7, 9-18, 20, 23, 24, 27-29, 31-35, 37, 42-46, 48-51, 55, 58-60
S. Group B *(agalactiae)*	≤0.03	≤0.015-0.25	402	≤0.008-0.5	7, 9, 14-17, 20, 21, 24, 27-29, 33, 35, 39, 40, 43
S. Group C			10	≤0.016-0.03	14, 43
S. Group G	0.016	0.016-≤0.03	32	0.008-0.03	14, 43
S. Groups C, F, G	0.03	0.03-0.5	43	≤0.01-0.5	7, 16, 24

[a] Number of strains
[b] Methicillin/oxacillin susceptibility unspecified
[c] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 3 of 7)

Organism	Median MIC_{50}	MIC_{90} Range	N[a]	MIC Range	References
Gram-Positive (cont)					
S. intermedius	0.05	0.05	25	≤0.025-0.2	8
S. mitis	0.4	0.4-3.1	27	0.016-6.25	8, 14
S. pneumoniae[b]	0.1	0.03-8	744	≤0.002-8	1, 2, 9-13, 17, 18, 23, 24, 27-31, 33, 35, 37, 42-51, 58-61
penicillin-susceptible	0.125	≤0.06-0.1	858	0.008-1	7, 14-16, 20, 32, 34, 53, 55, 62-66
penicillin-intermediate	4	1-4	319	0.015-16	16, 20, 53, 55, 62, 63, 65, 66
penicillin-resistant	8	2-16	404	≤0.03->16	7, 14-16, 20, 55, 62-66
S. salivarius	≤0.025	≤0.025	10	≤0.025	8
S. sanguis	0.05	0.05	31	≤0.025-0.2	8
Streptococcus spp	1	0.25-8	170	0.008->100	15, 19, 27, 38, 57
Viridans group streptococci[d]	4	0.06-16	172	≤0.008-64	1, 7, 16, 24, 33, 35
Gram-Negative (Nonenterobacteriaceae)					
Achromobacter xylosoxidans			2	>16	7
Acinetobacter calcoaceticus					
A. baumannii complex	4	4-8	41	0.25-16	14
A. johnsonii	4	4	12	0.1-8	14
A. lwoffi	2	2	20	0.5-4	14
A. radioresistans			6	0.25-2	14
Acinetobacter spp	8	1->128	488	0.03->128	2, 7, 12-14, 16, 17, 21, 22, 30, 33-36
Aeromonas hydrophila	0.5	0.5	72	≤0.03->16	7, 24, 36, 52
Aeromonas spp	0.5	0.5	22	0.1-0.5	33
Bordetella pertussis	12.5	12.5-100	68	4->100	1, 10, 14
Brucella spp			5	0.13-0.25	14

[a] Number of strains
[b] Penicillin susceptibility unspecified
[d] Includes penicillin-susceptible and -resistant strains
• References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 4 of 7)

Organism	Median MIC_{90}	MIC_{90} Range	N*	MIC Range	References
Gram-Negative (Nonenterobacteriaceae) (cont)					
Burkholderia cepacia	25	12.5->100	121	0.1->100	2, 7, 14, 23, 24, 44
Chlamydia pneumoniae			3	>80->100	67
Eikenella corrodens			1	0.1	8
Flavobacterium spp			2	>16	7
Haemophilus influenzae	0.5	0.1-12.5	2035	≤0.015-25	1, 2, 7, 10-15, 17, 18, 20, 23, 24, 27-31, 33, 34, 37, 42-51, 53, 55, 57-61, 64, 68-71
H. parainfluenzae	0.05	0.25-1	62	0.03-1	14, 15, 31, 71
Helicobacter pylori	2	2	16	0.5-2	14
Legionella spp	4	4->8	23	0.1->8	20, 72
Moraxella catarrhalis	0.25	≤0.06-16	1088	≤0.01-32	1, 7, 8, 11-20, 23, 24, 27-34, 37, 42-44, 46-49, 51, 53, 55, 58-61, 69, 73
Neisseria gonorrhoeae	≤0.025	≤0.008-0.25	503	0.001-1	1, 7, 10, 14, 15, 17, 20, 24, 28, 30, 34, 37, 70, 74
N. meningitidis	0.016	0.015-≤0.025	48	0.004-0.5	1, 15, 16, 30
Pasteurella multocida			9	0.008-0.125	15
Pseudomonas aeruginosa	>100	>4->256	1282	0.25->256	1, 2, 7, 10, 11, 13, 14, 16-18, 21-24, 26, 27, 36, 39, 44, 52, 53
P. fluorescens	>64	>64	22	>16->64	7, 14
P. putida	>64	>64	22	>16->64	7, 14
P. stutzeri			8	4->64	14
Pseudomonas spp	>100	>4->128	102	≤0.03->128	21, 25, 30, 33, 38
Stenotrophomonas maltophilia	>32	>4->128	231	0.1->128	2, 7, 14, 16, 21, 24, 33, 36

* Number of strains
* References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 5 of 7)

Organism	Median MIC_{90}	MIC_{90} Range	N*	MIC Range	References
Enterobacteriaceae					
Citrobacter amalonaticus			2	1-16	7
C. diversus	0.25	0.25-4	141	≤0.015-64	7, 21, 22, 24, 28, 29
C. freundii	>100	4->128	726	≤0.03->128	1, 2, 7, 11, 13, 14, 16, 17, 21-24, 26, 28, 29, 32, 36, 44
Citrobacter spp	64	>16->128	133	0.1->128	19, 25, 27, 30, 33-35, 52
Enterobacter aerogenes	>64	4->128	413	0.06->128	1, 7, 12-14, 16, 17, 21, 23-25, 28, 36
Pantoea agglomerans	0.5	0.5->4	31	≤0.03->4	7, 21
E. cloacae	>100	>4->128	1029	0.06->400	1, 2, 7, 10-14, 16, 17, 21, 23-26, 28, 29, 36, 43, 44, 49
E. sakazakii	0.25	0.25	13	0.06-2	7, 14
E. taylorae			2	16->16	7
Enterobacter spp	>16	2->128	347	0.06->128	16, 19, 21, 22, 27, 30, 32-35, 37, 38, 52, 53
Escherichia coli	0.5	0.25-64	3248	0.008-128	1, 2, 7, 10-14, 16-37, 39, 40, 42-50, 52, 53, 60, 68
Hafnia alvei	4	4-32	39	0.25-64	7, 14, 33, 52
Klebsiella oxytoca	0.25	0.03->100	559	≤0.008-128	1, 8, 10, 11, 14, 16-18, 20-24, 29, 32, 36, 51, 52
K. ozaenae			5	0.06->16	7, 52
K. pneumoniae	0.4	0.1-3.1	1591	≤0.01->128	1, 2, 10-14, 16-18, 20-26, 29, 32, 36, 39, 43, 44, 46, 49, 50, 52, 53, 55, 60, 68
Klebsiella spp	0.5	0.25-128	322	0.008->128	7, 19, 27, 28, 30, 33-35, 37, 38
Morganella morganii	32	2->128	690	0.004->128	1, 2, 7, 10-14, 16, 17, 20-24, 26, 29, 30, 32, 36, 51-53
Proteus mirabilis	0.1	0.06-25	1224	≤0.01-100	1, 2, 7, 10-14, 16-18, 20-30, 32, 36, 43, 49, 53, 68
P. penneri			5	0.06-2	14, 16
Proteus spp	0.25	0.125-100	94	≤0.01->100	19, 34, 37, 44
P. vulgaris	12.5	2->128	594	≤0.03->128	1, 2, 7, 10-14, 16-18, 20-26, 28-30, 32, 43, 52
Providencia alcalifaciens			1	0.008	20
P. rettgeri	3.1	0.5-50	315	≤0.006->128	1, 2, 7, 10-14, 17, 20-24, 29
Providencia spp	1	0.25-16	122	≤0.01->128	16, 22, 28, 30, 33, 52, 53
P. stuartii	3.1	2-64	144	≤0.015-64	1, 7, 10, 14, 17, 20, 24, 29

* Number of strains
• References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 6 of 7)

Organism	Median MIC_{50}	MIC_{50} Range	N*	MIC Range	References
Enterobacteriaceae (cont)					
Salmonella enteritidis	0.1	0.1-0.25	20	0.06-0.5	7, 68
S. typhi			2	0.06-0.1	7
Salmonella spp	0.5	0.2-1	444	≤0.01-16	14, 16, 24, 28-30, 32, 34-37, 39, 52
Serratia liquefaciens	64	64->64	29	0.5->128	7, 14, 22
S. marcescens	>100	1.9->128	913	0.1->128	1, 2, 7, 8, 10-14, 16, 17, 21-26, 28, 29, 35, 36, 39, 44, 53
Serratia spp	>16	4->128	152	0.03->128	16, 19, 21, 30, 32, 33, 52
Shigella spp	0.25	0.1-1	243	≤0.01-8	7, 14, 16, 24, 28-30, 32, 34, 36, 37, 39, 52
Yersinia enterocolitica	0.5	0.5-16	94	0.06-32	7, 14, 16, 24, 28, 29, 68
Anaerobes					
Bacteroides capillosus			2	0.2-1.6	8
B. fragilis group	>100	>16->200	320	≤0.05->200	1, 2, 7, 10, 15, 17, 23, 24, 27, 30, 44, 75
B. thetaiotaomicron	200	200	11	25->200	75
B. uniformis	200	200	13	1.6->200	75
Bacteroides spp	3.1	1->64	56	≤0.025->64	14, 15, 24, 75
Clostridium difficile	>64	>64-100	38	25-100	14, 75
C. perfringens	0.8	0.5-2	67	0.1-8	1, 15, 17, 24, 27
Clostridium spp	32	32	23	0.125-32	14, 15, 30
Eubacterium limosum			1	≤0.025	8
Fusobacterium nucleatum	1.6	1.6	32	0.008-3.1	1, 8, 15, 24
Peptococcus spp	1	1	10	0.06-4	24

* Number of strains
• References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 2. Summary of In Vitro Antibacterial Activity of Cefdinir
(Page 7 of 7)

Organism	Median MIC_{90}	MIC_{90} Range	N*	MIC Range	References
Anaerobes (cont)					
Peptostreptococcus anaerobius	0.8	0.8	28	≤0.025-12.5	8, 40, 75
P. asaccharolyticus	0.2	0.2	39	≤0.025-0.4	8, 75
P. magnus	0.4	0.4	51	≤0.025-16	8, 14, 40, 75
P. micros	≤0.025	≤0.025	16	≤0.025-0.1	8
P. prevotii			6	≤0.025-0.1	8
Peptostreptococcus spp	1	1	18	0.016-8	8, 15
Porphyromonas gingivalis			2	0.2-0.4	8
Prevotella bivia	12.5	12.5	21	≤0.25-25	40, 75
P. intermedia			8	0.2-0.8	8
P. oralis			1	0.4	8
Propionibacterium acnes			8	0.015-1	24
Propionibacterium spp			5	0.008-0.025	15

* Number of strains
♦ References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

TABLE 3. In Vitro Antibacterial Activity of Cefdinir Compared to Amoxicillin, Augmentin, Cefaclor, and Cefpodoxime Against Organisms Commonly Associated With Respiratory Tract and Skin Infections

Organism	Minimal Inhibitory Concentration (MIC) (μg/mL)									
	Cefdinir		Amoxicillin		Augmentin		Cefaclor		Cefpodoxime	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Staphylococcus aureus Methicillin/oxacillin-susceptible	0.25	0.5	0.8	1.6	0.4	1	2	6.25	2	4
Streptococcus pyogenes	≤0.025	≤0.03	≤0.025	≤0.025	≤0.025	0.03	0.125	0.25	≤0.025	0.03
S. pneumoniae Penicillin-susceptible	0.06	0.125			0.015	0.03	0.5	0.5	0.03	0.06
Haemophilus influenzae	0.25	0.5	0.5	1	0.25	0.5	4	8	0.06	0.1
Moraxella catarrhalis	0.13	0.25	1.6	4	0.1	0.25	1	2	0.25	0.5
Escherichia coli	0.25	0.5	6.25	>100	4	16	2	6.25	0.4	0.5
Klebsiella pneumoniae	0.1	0.4	100	>100	2	8	1	6.25	0.2	0.5

Data is generated from references 1, 2, 5, 7-75 list of which is depicted on pages 2-26 in volume 47 of the submitted NDA 50-739.

The labeling submitted by the sponsor includes the following organisms in the efficacy list:

Each of the microorganisms in the *in vitro* activity list will be discussed below along with the reason for including it or excluding it from the label.

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commercial

information

In the label the list of *in vitro* organisms with MIC_{90} values of ≤1 μg/mL should, therefore, read as follows:

C. Effects of Miscellaneous Factors on Activity

1. Effect of Inoculum Size

Several investigators have studied the effect of inoculum size on the activity of cefdinir. The results vary with the nature of the strains tested, especially with regard to the potency and spectrum of the β-lactamase produced by the test microorganisms

In one study by Neu, H.C. et al., cefdinir MICs increased with larger bacterial inocula (10^5 vs 10^7 CFU/mL) for both gram-positive and gram-negative species. The average increase was 2- to 4-fold (1-2 tube dilutions) for *E. coli* and *S. aureus*; 5- to 8-fold for *K. pneumoniae, C. freundii,* and *E. faecalis*; and 32-fold for *E. cloacae* (Table 4).

In another study by Fernandez-Roblas,R. et al., cefdinir MICs did not change at higher inocula (10^5 vs 10^7 CFU/mL) for 2 species - *H. influenzae* and *S. aureus*; increased only 2- to 4-fold for *E. coli, Y. enterocolitica, S. enteritidis*; and higher increases were observed at 8-fold for *K. pneumoniae* and 64-fold for *P. mirabilis* (Table 5).

In an agar dilution study by Briggs, B.M et al., the effect of inoculum size (10^4 vs 10^6 CFU/spot) was determined against β-lactamase-producing bacteria (Table 6). Again, the degree of diminished activity was associated with the strain of microorganism, and more specifically, with the nature of the β-lactamase produced. Among these isolates, *E. coli* and *S. aureus* were the least affected by 100-fold increases in the inoculum size per spot.

The lack of inoculum effect with *S. aureus* is further exemplified by the data from Cohen, M.A. et al. shown in Table 7. Regardless of the β-lactamase type produced by the microorganism, the activity of cefdinir was virtually undiminished.

Similarly, in a study by Martin, R. and Linares, J., there was no significant inoculum effect evidenced in *Streptococcus pneumoniae* strains (Table 8).

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TABLE 4. Effect of Inoculum Size

Organism	No.	Geometric Mean Cefdinir MIC (μg/mL) (Range)			
		10^6 CFU/mL		10^7 CFU/mL	
Escherichia coli	5	0.25	(0.12-0.5)	0.84	(0.25-2)
Klebsiella pneumoniae	5	0.16	(0.03-2)	1.14	(0.06-32)
Enterobacter cloacae	5	3.03	(1-16)	97	(16->128)
Citrobacter freundii	5	4	(0.25-64)	24.2	(8-64)
Staphylococcus aureus	5	0.44	(0.25-0.5)	0.76	(0.25-1)
Enterococcus faecalis	5	3.48	(2-4)	18.4	(8-32)

TABLE 5. Effect of Inoculum Size on the In Vitro Activity of Cefdinir Against Different Clinical Isolates

Organism	N	MIC_{100} (μg/mL)	
		10^5 CFU/mL	10^7 CFU/mL
Escherichia coli	10	0.5	1
Proteus mirabilis	10	0.06	4
Yersinia enterocolitica	10	0.5	2
Salmonella enteritidis	10	0.25	0.5
Klebsiella pneumoniae	10	0.12	1
Haemophilus influenzae	10	0.25	0.25
Staphylococcus aureus MRSA	5	1024	1024
S. aureus MSSA	5	0.5	0.5

TABLE 6. Effect of Inoculum Size on Cefdinir MICs Against β-Lactamase-Producing Bacteria

Organisms/Mechanisms of Resistance	Agar Dilution MICs (μg/mL)	
	10^4 CFU/Spot	10^6 CFU/Spot
Acinetobacter anitratus	2	16
Enterobacter aerogenes, Type 1[a]	8	>16
Enterobacter cloacae, Type 1a (P99)	>16	>16
Hafnia alvei, Type 1	16	>16
Morganella morganii, Type 1	4	>16
Providencia stuartii, Type 1	1	>16
Serratia liquefaciens, Type 1	0.5	2
Serratia marcescens, Type 1	>16	>16
Escherichia coli, TEM-1	0.12	0.12
E. coli, TEM-2	0.12	0.12
E. coli, HMS-1	0.25	0.25
E. coli, OXA-1	0.25	0.5
E. coli, OXA-2	0.25	0.25
E. coli, OXA-3	0.12	0.25
E. coli, SHV-1	0.12	0.12
E. coli, ATCC 25922	0.25	0.25
Klebsiella oxytoca, Type IVc (K1)	2	>16
K. oxytoca, Type IVc (K14)	2	>16
Klebsiella pneumoniae, wild type	0.12	0.12
K. pneumoniae, ExSpBL[b]	4	>16
K. pneumoniae, ExSpBL[b]	1	>16
Staphylococcus aureus, Penase	0.5	0.5
S. aureus, ATCC 29213	0.5	0.5

[a] β-Lactamase type

[b] Extended-spectrum β-lactamase

TABLE 7. Cefdinir Activity Against Standard and Heavy Inocula with β-Lactamase-Producing *Staphylococcus aureus* Strains

S. aureus Strain	β-Lactamase Type	MIC μg/mL of Cefdinir	
		10^5 CFU/mL	10^7 CFU/mL
PC-1	A	0.25	0.5
NCTC 9789	A	0.25	0.5
VU 94	A	0.25	0.25
22260	B	0.25	0.25
ST 79/741	B	0.5	0.5
V 137	C	0.5	0.5
FAR 8	D	0.25	0.25
FAR 10	D	0.25	0.25
SA-1	β-Lactamase negative	0.25	0.5

TABLE 8. Cefdinir Antibacterial Activity at Standard and High Inoculum Sizes Against *Streptococcus pneumoniae*

Penicillin-Susceptibility (No. of isolates)	MIC_{90} of Cefdinir (μg/mL)	
	10^5 CFU/mL	10^7 CFU/mL
Susceptible (30)	≤0.06	0.12
Intermediate (40)	4	4
Resistant (30)	8	16

2. Effect of Medium, pH, Horse and Human Serum, Urine, Sheep Red Blood Cells, 5% CO_2 Atmosphere, and Mg^{2+} on Antibacterial Activity

Several investigators studied the effects of culture medium, pH, horse and human serum, urine, sheep red blood cells, 5% CO_2, and Mg^{++} on *in vitro* results obtained with cefdinir.

In a study by Neu, H.C. et al., cefdinir was tested for MIC variance on different media (Mueller-Hinton broth vs agar; Mueller-Hinton, brain-heart infusion, and nutrient agars), across a pH range of 6 to 7.5. MICs were within a 2-fold range for all tests versus 5 strains each of *S. aureus, E. coli, K. pneumoniae, E. cloacae,* and *C. freundii*. Serum and urine did not alter the MICs or MBCs for *S. aureus, E. coli,* or *K. pneumoniae* (five isolates of each).

A second study by Mine, Y. et al., noted a 2- to 8-fold increase in MICs for *E. faecalis* due to medium effects (based on results obtained with sensitivity test agar versus heart infusion agar versus MHA).

In a study by Fernandez-Roblas, R. Et al., variations in culture medium had no effect on cefdinir MICs against 10 isolates each of *P. mirabilis* and *K. pneumoniae*. Susceptibilities were compared in Diagnostic Sensitivity Test Agar (DST) and MHA at pH 7.4. Respective MIC_{100} values and ranges for cefdinir were 0.12 μg/mL and 0.06 to 0.12 μg/mL for *P. mirabilis* in both media. Similarly identical in both media were the MIC_{100} and ranges for *K. pneumoniae* which were 0.5 μg/mL and 0.06 to 0.5 μg/mL, respectively. Another study by Nishino, T. Et al., compared heart infusion agar, nutrient agar, trypticase soy agar, and MHA with a similar outcome. MIC ranges (in μg/mL) for *S. aureus* 209P-JC, *E. coli* KC-14, *K. pneumoniae* KC-1, *P. vulgaris* OX-19, and *S. marcescens* T-55 were as follows: 0.05 to 0.2, 0.1 to 0.2, 0.05 to 0.2, 0.2 to 0.39, and 1.56 to 1.56, respectively.

Bacterial responses to cefdinir were unaffected by variations in pH. In a study by Fernandez-Roblas, R. Et al, changing the pH from 7.4 to 8.5 had no effect on the activity of cefdinir versus 10 strains of *P. mirabilis* and *K. pneumoniae* in either DST or MHA. (The MIC_{100} values and ranges obtained at pH 8.5 were virtually identical to those indicated above.). When compared in MHA, similar MICs were found for cefdinir at pH 5.4, 6.4, 7.4, and 8.4 (Mine, Y., et al.). MIC ranges (in μg/mL) were 0.025 to 0.05 for *S. aureus* 209p JC-1, 0.5 to 0.1 for *E. coli* NIHJ JC-2, and 0.05 to 0.1 for *K. pneumoniae* NCTC 418. In a study by Marchese, A. Et al., utilizing 14 staphylococcal isolates, no major MIC shifts occurred when the pH of Mueller-Hinton broth was varied between 5.5, 7.0, or 8.0. However, discrepant results were reported in another study by Nishino, T. et al. When tested in heart infusion agar at pH 5.5, the MIC for *S. marcescens* T-55 was 6.25 μg/mL, contrasted with MICs of 0.78 and 0.39 μg/mL at pH 7.0 and 8.5. The MIC ranges (in μg/mL) for *S. aureus* 209-P JC, *E. coli* KC-14, *K. pneumoniae* KC-1, and *P. mirabilis* OX-19 were as follows: 0.025 to 0.2, 0.2 to 0.39, 0.1 to 0.39, and 0.39 to 0.78.

In a study by Nishino, T. et al., no effects were demonstrated when cefdinir was tested in heart infusion agar to which 0%, 10%, 25%, and 50% horse serum had been added: MIC ranges (in μg/mL) were determined to be 0.1 to 0.2 for *S. aureus* 209-P JC, 1.56 to 3.13 for *E. coli* KC-14, 0.2 for *K. pneumoniae* KC-1, 0.39 to 0.78 for *P. vulgaris* OX-19, and 1.56 to 3.13 for *S. marcescens* T-55. In another series of experiments, the presence of 50% human serum had little effect on the activity of cefdinir against 25 clinical isolates consisting of 5 strains each of *S.*

aureus, S. pneumoniae, S. pyogenes, H. influenzae, and *M. catarrhalis,* producing at most a 2-fold increased MIC (Garcia-Rodriguez, J.A., et al.). When the susceptibility of 14 staphylococcal isolates was tested in 50% human serum or human urine, MIC values generally ganged by 2-fold (Marchese, A. et at.).

Buschelman, B.J., et al., demonstrated that the incorporation of 5% sheep blood in MHA produced a significant enhancement of the activity of cefdinir against *Enterococcus faecalis.* The mean zone diameter produced by 5-μg cefdinir disks against 30 *E. faecalis* isolates was 13.6 mm on MHA containing 5% sheep blood, but was 9.2 mm on unsupplemented MHA; only 2 isolates showed no increased zone diameters. Agar dilution MICs against 10 isolates were 0.5 to 2 μg/mL in MHA with 5% sheep blood (median 1 μg/mL), whereas all 10 had MICs of 2 μg/mL in MHA.

The following parameters had no significant effect on the antibacterial activity of cefdinir on MHA: 5% sheep red blood cells, 5% CO_2, and a Mg^{++} content tenfold greater than that found in normal agar (Briggs, B.M., et al.). These results are shown in Table 9.

TABLE 9. Cefdinir Activity in 5% Sheep Red Blood Cells (SBC), 5% CO_2 Atmosphere, and High Mg^{++} Content (10× Greater Than Normal Agar)

Organism	MIC μg/mL of Cefdinir			
(Number of Strains)	None	5% SBC	5% CO_2	Mg^{++}
A. anitratus	2	8	4	4
M. morganii	4	4	4	4
P. stuartii	1	2	4	2
S. liquefaciens	0.5	0.5	2	0.5
E. coli (8)	0.25	0.25	0.25	0.25
K. oxytoca (2)	2	2	4	2
K. pneumoniae	0.12	0.12	0.12	0.12
K. pneumoniae	4	8	8	4
K. pneumoniae	1	1	2	1
S. aureus (2)	0.5	0.5	0.25	0.5

In summary, modifications in susceptibility test conditions are generally not expected to have any significant effects on *in vitro* results obtained with cefdinir. These include culture medium, pH,

horse and human serum, urine, sheep red blood cells, 5% CO_2, and Mg^{++}. However, the inclusion of 5% sheep blood in Mueller-Hinton Agar (MHA) appeared to enhance the activity of cefdinir against isolates of *Enterococcus faecalis*.

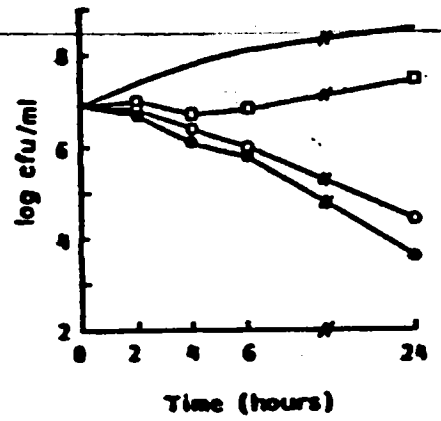
D. Bactericidal Activity

The bactericidal activity of cefdinir has been demonstrated by several investigators.

In a study by Mine, Y. et al. the mean MIC and MBC of cefdinir against *S. aureus* 2558 were 0.39 (range = 0.1-1.56) and 17.7 (range = 12.5-25) μg/mL and against *E. coli* 3147 the mean MIC and MBC were 0.33 (range = 0.2-0.78) and 0.66 (range = 0.2-3.13) μg/mL respectively. The bactericidal concentrations were 4× MIC for *S. aureus* and 1× MIC for *E. coli*. A greater than 3 log decrease in CFU/mL (colony forming units) was seen (Figures 1 and 2) between 6 and 24 hours for *S. aureus* 2558 and *E. coli* 3147. No regrowth was seen up to 24 hours of incubation. In other studies, similar kill curves have been obtained with *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, E. coli,* and *S. pyogenes* (see references 4, 47, 63, 69, 74, and 76 listed on pages 2-26 in volume 47 of the submitted NDA 50-739).

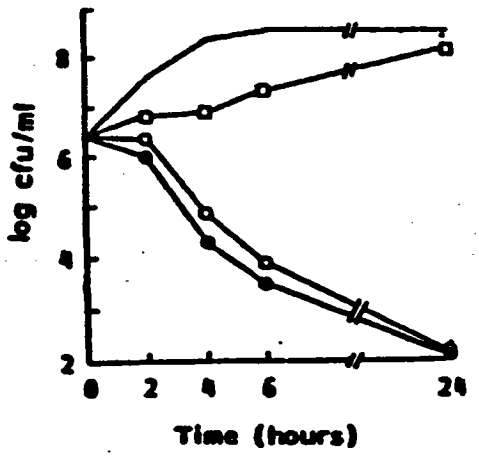
Cefdinir was generally bactericidal against *S. pneumoniae, S. aureus, S. epidermidis, S. hominis, S. xylosus, S. haemolyticus, S. saprophyticus, S. capitis, H. influenzae, M. catarrhalis,* and *E. coli* (Table 10) and bacteriostatic against *P. mirabilis, E. cloacae,* and *C. freundii*. Cefdinir was bactericidal against *S. aureus* in 3 of 4 studies and bactericidal against *K. pneumoniae* in 1 of 2 studies. These discrepancies may represent either a methodological variation or a strain dependency.

In a study by Briggs, B.M. et al., the production of β-lactamase did not influence the degree of bactericidal action of cefdinir against *E. coli, K. oxytoca,* and *K. pneumoniae* (Table 11).



— Control, □ 1/4 MIC, ○ 1 MIC, ● 4 MIC

FIGURE 1. Bactericidal Activity of Cefdinir Against *Staphylococcus aureus* 2558.



— Control, □ 1/4 MIC, ○ 1 MIC, ● 4 MIC

FIGURE 2. Bactericidal Activity of Cefdinir Against *Escherichia coli* 3147.

TABLE 10. Comparison of MIC and MBC for Cefdinir

Organism	Ref[a]	No.[b]	MIC μg/mL		MBC μg/mL	
			Range	Geometric Mean	Range	Geometric Mean
S. pneumoniae	47	5	0.06-0.12	0.09	0.12-0.25	0.16
H. influenzae	47	5	0.5-1	0.57	0.5-2	1
	76	4	0.5-1	0.84	0.5-1	0.84
	70	100	0.06-1	0.5[c]	0.06-4	1[c]
M. catarrhalis	47	5	0.06-0.5	0.25	0.06-1	0.43
S. aureus	47	5	0.12-2	0.38	0.25-4	0.57
	1	8	0.1-1.56	0.39[d]	12.5-25	17.7[d]
	24	4	1-1	1	1-8	2.4
	54	3	0.25-1	0.5	0.5-1	0.79
S. epidermidis	54	4	0.03-0.5	0.18	0.06-0.5	0.29
S. hominis	54	2	0.25-0.5	0.35	0.5	0.5
S. xylosus	54	1	0.125	0.125	0.25	0.25
S. haemolyticus	54	1	1	1	2	2
S. saprophyticus	54	2	1-4	2	2-8	4
S. capitis	54	1	0.125	0.125	0.125	0.125
E. coli	47	5	0.12-0.25	0.22	0.12-0.5	0.38
	1	8	0.2-0.78	0.33[d]	0.2-3.13	0.66[d]
	24	4	0.12-0.5	0.25	0.2-1	0.35
K. pneumoniae	1	6	0.2-0.78	0.35[d]	6.25-12.5	8.85[d]
	24	5	0.03-1	0.22	0.06-2	0.25
P. mirabilis	1	5	0.2-0.39	0.23[d]	3.13-12.5	7.19[d]
E. cloacae	24	5	0.5-32	4.59	2-64	21.1
C. freundii	24	3	0.25-2	0.63	1-8	3.7

MIC = Minimum Inhibitory Concentration.

MBC = Minimum Bactericidal Concentration.

[a] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

[b] Number of strains

[c] Mean expressed as MIC_{90}

[d] Arithmetic mean

TABLE 11. Comparison of MIC and MBC of Cefdinir Against β-Lactamase-producing Strains of *E. coli*, *K. oxytoca*, and *K. pneumoniae*

Organism	Resistance Mechanism		Cefdinir Activity	
			MIC μg/mL	MBC μg/mL
E. coli	Type III	(HMS-1)	0.25	0.5
		(OXA-1)	0.5	1
		(OXA-2)	0.25	0.25
		(OXA-3)	0.12	0.25
		(SHV-1)	0.25	0.25
		(TEM-1)	0.5	0.5
		(TEM-2)	0.12	0.12
K. oxytoca	Type IV	(K1)	4	4
		(K14)	4	4
K. pneumoniae	Type III	(ExSpBL)	4	4
		(ExSpBL)	4	4

ExSpBL = Extended spectrum β-lactamase.

E. Postantibiotic Effect

Postantibiotic effect (PAE) refers to the recovery period or persistent suppression of bacterial growth after short antimicrobial exposure. It is generally accepted that a prolonged PAE will extend the chemotherapeutic action of an antimicrobial drug beyond the time that the agent is available in inhibitory concentrations at the site of infection in the host. The results of three studies by Blandino, G., Marchese, A., Howard, B.M.A. and their coworkers are summarized in Table 12. Cefdinir PAEs for species of staphylococci were generally in the 1- to 2-hour range, although in a few cases they were as low as 0.2 to 0.7 hours or as high as 3 to 4.3 hours. Species included *S. aureus*, *S. epidermidis*, *S. hominis*, *S. xylosus*, *S. haemolyticus*, *S. saprophyticus*, and *S. capitis*. Demonstrating similar PAEs were *Streptococcus pneumoniae* and *S. pyogenes*. The gram-negative respiratory tract pathogens *Haemophilus influenzae* and *Moraxella catarrhalis* also demonstrate PAEs, but to a lesser extent (0.4-0.9 hours). PAEs obtained with the enteric gram-negative rods *Escherichia coli* and *Klebsiella pneumoniae* were unpredictable. –

TABLE 12. Cefdinir Postantibiotic Effect (PAE)

Organism	No. of Strains	Fold MICs	Exposure Time (hr)	PAE Range (hr)	Reference[a]
Staphylococcus aureus	5	2	2	0.8-1.5	47
	5	4	2	1.1-1.4	47
	3	4	1	0.8-1	54
	1	1	1	2.1	78
	1	1	3	2.5	78
	1	4	1	0.4	78
	1	4	3	>4.3	78
S. epidermidis	3	4	1	0.2-1.8	54
S. hominis	2	4	1	1.7-2	54
S. xylosus	3	4	1	0.4-2	54
S. haemolyticus	3	4	1	2-4.1	54
S. saprophyticus	2	4	1	0.7-1.3	54
S. capitis	3	4	1	1.5-3	54
Streptococcus pneumoniae	5	2	2	0.5-1	47
	5	4	2	0.9-1.1	47
S. pyogenes	1	1	1	0.4	78
	1	1	3	3.8	78
	1	4	1	0.6	78
	1	4	3	3.8	78
Haemophilus influenzae	5	2	2	0.4-0.7	47
	5	4	2	0.4-0.8	47
Moraxella catarrhalis	5	2	2	0.5-0.7	47
	5	4	2	0.6-0.9	47
Escherichia coli	5	2	2	0.3-0.6	47
	5	4	2	0.5-0.7	47
	1	1	1	0.4	78
	1	1	3	-1.6	78
	1	4	1	0.1	78
	1	4	3	-1	78
Klebsiella pneumoniae	1	1	1	-1.4	78
	1	1	3	-0.6	78
	1	4	1	-1.3	78
	1	4	3	-0.7	78

[a] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

F. Antibacterial Interaction Studies *In Vitro*

Combination activities of cefdinir with other antibacterial drugs were assessed by standard checkerboard titration and time-kill curves in a study by Marches, A. et al. A total of 18 strains of the following species were tested: *S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis,* and *S. xylosus.* Penicillin-resistant isolates were included. The other antibiotics were ciprofloxacin, netilmicin, fosfomycin, rifampicin, teichoplanin, vancomycin, and clarithromycin.

Based on the standard fractional inhibitory concentration (FIC) index of data derived from checkerboard combination MICs, the most common outcome was indifference. Synergism was detected in 11 of 175 drug cefdinir combinations with other antibiotics, and antagonism was not found.

A similar outcome was evident when the interaction of cefdinir with the same antibiotics was evaluated employing the time-kill system. Indifference occurred in the majority of the combinations tested. Synergy was observed more frequently with the time-kill method in 25 of 126 combinations of drugs studied. Synergy was more common with cefdinir and teicoplanin (8 of 18 strains studied). Synergy was also produced with rifampicin (4) and vancomycin (4), fosfomycin (3) and 2 each by the remaining 3 antibiotics. Again, antagonism was not found.

These *in vitro* data indicate that no deleterious effects on the antibacterial activity of cefdinir should be anticipated when it is used in conjunction with other antibiotics.

G. Enzyme Hydrolysis Rates

A major component of the lack of susceptibility of bacteria to cephalosporins is associated with the β-lactamases produced by these microorganisms. Cefdinir and other cephalosporins have been developed which are stable to attack by β-lactamase.

Cefdinir has been shown to be stable to the hydrolytic activity of a variety of β-lactamases of plasmid or chromosomal origin including the following types (Richmond-Sykes types in parentheses) of penicillinases, cephalosporinases (including cefotaximases, ceftazidimases, and oximinocephalosporinases), and extended spectrum β-lactamases:

BIL-1	TEM-1 (IIIa)	SHV-1 (IIIa)
CAZ-2	TEM-2 (IIIa)	SHV-2
K-1 (IV)	TEM-4	SHV-3
MEN-1	TEM-6	SHV-4/CAZ-5
OXA-2 (V)	TEM-7	SHV-5/CAZ-4
OXA-4	TEM-9	
	TEM-10	Sabath-Abraham (Id)
P99 (Ia)		
PC-1	TEM-E1	
PSE-1 (V)	TEM-E2	
PSE-3 (V)	TEM-E3	
PSE-4 (V)	TEM-E4	

These enzymes have been detected in a variety of species including *S. aureus, H. influenzae, M. catarrhalis, N. gonorrhoeae, C. freundii, E. cloacae, E. coli, K. oxytoca, K. pneumoniae, M. morganii, P. mirabilis, P. vulgaris, S. marcescens, P. aeruginosa, P. cepacia, S. maltophilia,* and *B. fragilis*. Supporting data are contained in Tables 13 through 19.

The study of Neu, H.C. et al. is summarized in Table 13: cefdinir was stable to a number of isolated gram-negative β-lactamases including TEM-1 and -2 (the most common plasmid

β-lactamases), *Enterobacter cloacae* chromosomal P99 (Richmond-Sykes Ia), *Klebsiella oxytoca* K1 (Richmond-Sykes IV), and *Moraxella catarrhalis* (. Cefdinir was also stable to hydrolysis by the PC-1 β-lactamase from *S. aureus*. TEM-3 β-lactamase hydrolyzed cefdinir as did both PSE-2 and OXA-2. *S. maltophilia* β-lactamase also hydrolyzed cefdinir as did *P. vulgaris* enzyme.

Cefdinir was more stable to penicillinases than cefaclor. Mine, Y. et al. demonstrated that the stability of cefdinir to cephalosporinases was dependent on the type, being relatively stable to Types Ia and Ib while less stable to Types Ic and Id and a cefuroximase (Table 14). Tomatsu, K. And coworkers demonstrated that cefdinir showed sensitivity to hydrolysis by the oxyiminocephalosporinases (Table 15).

Cefdinir has a β-lactamase stability profile generally better than that of cefaclor and cefuroxime (Tables 14-19). When compared to cefixime, cefdinir shows greater sensitivity to some gram-negative cephalosporinases (Table 18).

Unlike cefaclor, cefdinir is generally stable to several of the new extended-spectrum β-lactamases of the following classes: cefotaximase, ceftazidimase, and cephalosporinase (Table 19).

TABLE 13. β-Lactamase Stability of Cefdinir

Source	Type	Richmond-Sykes Classification	Relative Rate[a] of Hydrolysis
Escherichia coli	TEM-1	IIIa	<0.1
Escherichia coli	TEM-2	IIIa	<0.1
Klebsiella pneumoniae	SHV-1	IIIa	3
Enterobacter cloacae	P99	Ia	<0.1
Morganella morganii		Ia	<0.1
Proteus vulgaris		Ic	8.7
Pseudomonas aeruginosa	Sabath-Abraham	Id	2.3
Klebsiella oxytoca	K1	IV	0.3
Pseudomonas aeruginosa	PSE-1	V	1.8
Pseudomonas aeruginosa	PSE-2	V	41.3
Pseudomonas aeruginosa	PSE-3	V	<0.1
Pseudomonas aeruginosa	PSE-4	V	<0.1
Pseudomonas aeruginosa	OXA-2	V	20.4
Staphylococcus aureus	PC-1		<0.1
S. maltophilia			6.1
Escherichia coli	TEM-3		15.5
Enterobacter aerogenes			14
Serratia marcescens			17.6
Klebsiella pneumoniae			10.9
Moraxella catarrhalis			<0.1

[a] Relative to cephaloridine as 100%

TABLE 14. Stability of Cefdinir, Cefixime, and Cefaclor to β-Lactamases

Source	Type[b]	Relative Rate of Hydrolysis[a]		
		Cefdinir	Cefixime	Cefaclor
Serratia marcescens FP1184	CSase Ia(1)	3.2	4.4	140
Enterobacter cloacae FP1185	CSase Ia(2)	0.5	0.3	45
Escherichia coli FP1186	CSase Ib	3.5	1.0	102
Proteus vulgaris FP1187	CSase Ic	26.5	2.6	292
Pseudomonas aeruginosa FP1380	CSase Id	17.8	0.9	31
Bacteroides fragilis FP786	CXase	319.6	12.0	46
Proteus mirabilis FP240	PCase II	<0.1	<0.1	0.1
Escherichia coli FP1189	PCase III	0.1	0.4	2.7
Klebsiella pneumoniae FP239	PCase IV	0.1	<0.1	3.2
Pseudomonas aeruginosa FP1190	PCase V	1.0	0.1	0.3
Staphylococcus aureus FP1191		<1.0	<1.0	2.2

[a] Percent of hydrolysis of cephaloridine for cephalosporinase; ampicillin for penicillinase
[b] CSase = cephalosporinase; PCase = penicillinase; CXase = cefuroximase.

TABLE 15. Stability of Cefdinir and Cefuroxime to β-Lactamases Produced by Gram-Negative Bacteria

Source	Type[b]	Relative Hydrolysis Rate[a]	
		Cefdinir	Cefuroxime
Escherichia coli ML1410 Rms 212	PCase	<1	<1
Citrobacter freundii GN7391	CSase	<1	<1
Enterobacter cloacae GN7471	CSase	<1	<1
Morganella morganii 1510	CSase	1.2	3.1
Bacteroides fragilis 308	OCase	13	52
S. maltophilia GN12873	OCase	18	4.3
Proteus vulgaris GN7919	OCase	10	152
Pseudomonas cepacia GN11164	OCase	2.2	99

[a] Relative to cephaloridine as 100%.
[b] Pcase = penicillinase; Csase = cephalosporinase; Ocase = oxyiminocephalosporinase.

TABLE 16. Stability of Cefdinir, Cefixime, and Cefuroxime to β-Lactamases

β-Lactamase Type	Relative Efficiency of Hydrolysis[a]		
	Cefdinir	Cefixime	Cefuroxime
TEM-1	<0.1	<0.1	<0.1
TEM-3	18.9	10.8	82.7
TEM-5	1.1	0.4	1.9
TEM-9	3.7	7.7	5.1
SHV-1	<0.1	<0.1	<0.1
SHV-2	1.3	1.2	9.2
K-1[b]	0.2	0.07	10.3

[a] Vmax
[b] β-Lactamase derived from *K. pneumoniae*, all others derived from *E. coli*

TABLE 17. Stability of Cefdinir, Cephalexin, Cefuroxime, and Cefixime to Extended-Spectrum β-Lactamases

Extended-Spectrum β-Lactamase	Relative Rate of Hydrolysis[a]			
	Cefdinir	Cephalexin	Cefuroxime	Cefixime
BIL-1	NM[c]	100	NM	NM
SHV-2	0.63	11	5.4	1.8
SHV-3	0.5	11.2	5.6	2.1
SHV-5	1.1	25	3.8	3.9
TEM-1[b]	NM	0.72	NM	NM
TEM-3	21	151	95	284
TEM-4	8.8	83	19	21
TEM-5	96	37	102	124
TEM-6	1.8	19	7.7	9.5
TEM-7	0.44	1.5	0.7	0.8
TEM-10	1.5	3.0	2.0	12
TEM-E1	5.3	26	5.4	12
TEM-E2	0.23	3.19	NM	13
TEM-E3	2.4	5.3	95	28
TEM-E4	4.2	12.5	1.3	0.37

[a] Relative Vmax value compared to ampicillin at 100
[b] Control narrow range of β-lactamase
[c] Rate of hydrolysis not measurable

TABLE 18. Stability of Cefdinir, Cefaclor, Cephalexin, Cefuroxime, and Cefixime to Hydrolysis by β-Lactamases

Source of β-Lactamase (Type)	Rate of Hydrolysis[a]				
	Cefdinir	Cefaclor	Cephalexin	Cefuroxime	Cefixime
M. catarrhalis M184	3	27	3	1	1
S. aureus B25	10	1511	92	7	6
N. gonorrhoeae 250	6	43	5	2	1
H. influenzae 49	3	39	7	2	2
E. coli (TEM-1)	1	52	1	–[b]	0.02
E. coli (TEM-2)	4	188	11	1	2
E. coli (TEM-7)	3	44	1	1	3
E. coli (TEM-10)	6	26	4	3	8
E. coli (SHV-1)	3	120	14	3	1
E. coli (SHV-2)	6	111	17	7	4
E. coli (SHV-5)	2	240	35	11	2
E. coli (CAZ-2)	9	26	5	4	18
E. coli (OXA-2)	1	9	–	–	1
E. coli (OXA-4)	1	3	–	–	0.2
E. coli (PSE-1)	2	29	3	–	2
E. cloacae 55M (Ia)	14	9167	2817	1	10
P. aeruginosa 164cd (Id)	12	506	190	1	3
K. oxytoca M229 (IV)	20	868	148	161	3

[a] N moles substrate hydrolyzed per minute per milligram

[b] Hydrolysis <0.01

TABLE 19. Stability of Cefdinir, Cefixime, and Cefaclor to Extended-Spectrum β-Lactamases

Extended Spectrum β-Lactamase Class	Type or Source	Relative Rate of Hydrolysis[a]		
		Cefdinir	Cefixime	Cefaclor
Cefotaximase	SHV-2	1.2	2.0	19
	TEM-3	25	25	140
	MEN-1	1.7	low[b]	230
Ceftazidimase	SHV-4	1.0	3.9	18
	SHV-5	3.5	4.1	20
Cephalosporinase	*E. coli*	low	low	134
	M. morganii	low	low	103
	P. vulgaris	low	low	17,500

[a] Vmax

[b] Rate of hydrolysis too low to determine

H. Assessment of Resistance

1. Mechanisms of Resistance

Resistance to β-lactam antibiotics is primarily due to the production of inactivating enzymes (β-lactamases) by both gram-positive and gram-negative bacteria. Two less common types of β-lactam resistance are reduced or inhibited uptake of the molecule, or alteration of the target PBPs by mutation.

Due to its chemical structure, cefdinir is able to resist enzymatic hydrolysis by the most commonly found β-lactamases (see Section G, Enzyme Hydrolysis Rates). Cefdinir also functions as an inhibitor of these enzymes, as shown by Neu, H.C. et al (Table 20). However, Jacoby, G.A. and coworkers have revealed that the activity of cefdinir and other cephalosporins can be decreased by coupling diminished uptake in specifically constructed porin-deficient mutants which have an enhanced expression of β-lactamase production.

TABLE 20. Inhibition of β-Lactamases by Cefdinir

β-Lactamase	Source Organism	Richmond-Sykes Classification	% Inhibition of β-Lactamase Hydrolysis[a]
TEM-1	*Escherichia coli*	IIIa	41
P99	*Enterobacter cloacae*	Ia	92.2
	Morganella morganii	Ia	100
Sabath-Abraham	*Pseudomonas aeruginosa*	Id	100
K1	*Klebsiella oxytoca*	IV	98.5
PSE-2	*Pseudomonas aeruginosa*	V	23.3
OXA-2	*Pseudomonas aeruginosa*	V	16.6
PC-1	*Staphylococcus aureus*		16.6

[a] For PSE-2, OXA-2, and PC-1, 100 μM cephaloridine was used as the substrate; for the other β-lactamases, 100 μM nitrocefin was used as the substrate.

Data regarding the frequency of resistant mutants among susceptible populations and patterns of multistep development of resistance have been reported by Marchese, A. and Mine, Y. and their coworkers, respectively. The rate of development of spontaneous resistant mutants was determined with several species of *Staphylococcus: S. aureus, S. epidermidis, S. xylosus, S. saprophyticus, S. haemolyticus,* and *S. hominis*. The frequency of isolation of resistant clones was evaluated by seeding agar plates containing concentrations of cefdinir equivalent to 2×, 5×, and 10× MICs with very heavy bacterial inocula (10^8 to 10^{11} cells per mL). The plates were incubated for 48 hours at 37°C to permit the growth of single mutant cells into visible colonies. In general, the development of resistant strains was rare with all cefdinir concentrations used. At 5× MIC, the range of resistance frequencies was 2×10^{-8} down to 1×10^{-9}, and the range for 10× MIC was 6×10^{-8} to 2×10^{-9}.

As is characteristic of cephalosporins, cefdinir resistance development was slow and stepwise. After 14 transfers through increasing concentrations of cefdinir, the MIC against *S. aureus* 209P JC-1 was increased from 0.05 to 0.78 μg/mL. For *E. coli* 3147, the MIC was elevated from a baseline of 0.2 μg/mL to a 14-transfer value of 6.25 μg/mL. In contrast, *S. aureus* developed resistance more rapidly to cephalexin and cefaclor: pre- and posttransfer values were 1.6 and 100 μg/mL for the former, and 0.78 and 100 μg/mL for the latter. The 3 agents were similar against the *E. coli* strain, although cephalexin and cefaclor had higher initial and posttransfer MICs than did cefdinir.

In the study performed by Mine, Y. et al., in which an ampicillin-resistant plasmid was introduced

into *E. coli* CSH2, no change in the MICs of cefdinir was observed; however, a ≥4-fold increase in MICs was observed for cefaclor and amoxicillin.

2. Cefdinir Activity *In Vitro* Against β-Lactam-Resistant Bacteria

Cohen, M.A. and his coworkers demonstrated that one of the properties of cefdinir which differentiates it from other oral cephalosporins is its enhanced activity against *S. aureus*. In this study the MIC of cefdinir was 0.25 to 0.5μg/mL against strains of *S. aureus* producing each of the 4 recognized staphylococcal β-lactamases A, B, C, and D, as well as a β-lactamase-nonproducing control strain as shown in Table 21. Further, the MIC of cefdinir was not altered when the inoculum was increased from 5×10^5 to 5×10^7 CFU/mL. For other oral cephalosporins, these strains were less susceptible, and in some cases the susceptibility was further diminished by increasing the inocula.

TABLE 21. Cefdinir Activity Against β-Lactamase-Producing *S. aureus* Strains

β-Lactamase Type/ Inoculum Size (CFU/mL) 5×	MIC Range μg/mL[a]							
	Cefdinir	Cefaclor	Cefixime	Cefpodoxime	Cephalexin	Amoxicillin	Amoxicillin/ Clavulanate	Oxacillin
A/10^5	0.25	8-16	8-16	2	8	32->128	4-8	0.5-1
A/10^7	0.25-0.5	128	8-16	2	16	>128	64-128	1-4
B/10^5	0.25-0.5	4	16-32	2	4	8-16	4	0.5-1
B/10^7	0.25-0.5	16-32	16-32	2-4	8	64->128	32-128	1-2
C/10^5	0.25-0.5	4-8	4-32	1-4	8	32-128	4-16	0.5
C/10^7	0.25-0.5	16-64	8-32	2-4	8	>128	16-128	1-2
D/10^5	0.25	2	8	1-2	2	1-2	0.5-1	0.125-0.25
D/10^7	0.25	8	8-16	1-2	4-8	64->128	8-64	0.5
None/10^5	0.25	4	16	2	2	0.25	0.25	0.25
None/10^7	0.5	4	16	2	2	0.25	0.5	0.5

[a] There were 2 strains producing Type A β-lactamase, 2 each producing Types B, C, and D, and 2 nonproducer.

Several reports have documented the activity of cefdinir against β-lactamase-producing bacteria which are frequently found in community-acquired infections: *H. influenzae, M. catarrhalis, N. gonorrhoeae,* and *S. aureus*.[7,17,20,70] The data are summarized in Table 22. In these species, cefdinir susceptibility was not diminished by the production of β-lactamase.

TABLE 22. Cefdinir Activity Against β-Lactamase-Producing Isolates of *H. influenzae, M. catarrhalis, N. gonorrhoeae, S. aureus, S. epidermidis, S. saprophyticus, E. coli,* and *P. mirabilis*

Bacterial Species	Reference[d]	Activity vs Producers of β-Lactamase[a]			Activity vs Nonproducers of β-Lactamase		
		No.	MIC_{50}	MIC_{90}	No.	MIC_{50}	MIC_{90}
H. influenzae	17	16	0.06	0.25	16	0.06	0.25
	7	21	0.12	0.25	21[b]	0.12	0.25
	70	100	0.5	0.5	100	0.5	0.5
	20	24	0.25	1	20	0.25	0.5
M. catarrhalis	17	22	0.13	0.25	5	0.063	
	7	33	0.06	0.12	12	0.03	0.06
	20	20	0.25	0.25	9	0.125	
N. gonorrhoeae	17	10	<0.008	0.016	17	<0.008	<0.008
	7	14	≤0.03	≤0.03	20	≤0.03	≤0.03
	20	18	0.008	0.008	14	0.004	0.015
S. aureus[c]	17	31	0.5	0.5	29	0.25	0.5
	20	51	0.25	0.5	4	0.25	
S. epidermidis[c]	20	23	0.125	0.125	9	0.125	
S. saprophyticus[c]	20	12	0.25	0.5	10	0.25	0.25
E. coli	20	28	0.25	0.25	2	0.06	
P. mirabilis	20	10	0.125	0.125	24	0.06	0.125

[a] Activity expressed in μg/mL

[b] Excludes non-β-lactamase producers with intrinsic resistance to ampicillin (BLNAR)

[c] Excludes methicillin-resistant isolates

[d] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

In a study by Mine, Y. and colleagues, the activities of cefdinir and other β-lactams against a variety of β-lactam-resistant strains were investigated. The summary of the data appears in Table 23. Cefdinir was active against most ampicillin-resistant isolates at concentrations ≤1 μg/mL. These included ampicillin-resistant *E. coli,* as well as most isolates of *K. pneumoniae, S. aureus, P. mirabilis, H. influenzae, M. catarrhalis,* and *N. gonorrhoeae.* In several cases, cefdinir was markedly more potent than the cephalosporins cefaclor and cephalexin. None of the compounds was highly active against several of the cephalosporin-resistant *E. coli* strains or the methicillin-resistant *S. aureus.* The mechanisms by which the former resisted the activity of the cephalosporins were not elucidated in this study. The latter greatly owe their cephalosporin-resistance to a modified PBP and are generally not susceptible to any β-lactam antibiotic.

TABLE 23. Antibacterial Activity of Cefdinir, Cefixime, Cefaclor, Cephalexin, and Ampicillin Against β-Lactam-Resistant Strains

Organism (Number of Strains)	Mean MIC (μg/mL)				
	Cefdinir	Cefixime	Cefaclor	Cephalexin	Ampicillin
Methicillin-Resistant					
S. aureus (24)	7.7	>100	>100	>100	38.6
Cefaclor-Resistant					
E. coli (7)	13.8	18.6	82.2	100	>100
K. pneumoniae (5)	0.4	0.2	7.2	12.5	>100
Cephalexin-Resistant					
E. coli (10)	4.7	6.7	38.0	57.5	>100
K. pneumoniae (9)	0.5	0.2	3.7	15.8	>100
Ampicillin-Resistant					
S. aureus (40)	0.3	ND[a]	3.3	ND[a]	23.3
E. coli (14)	0.2	0.3	1.8	6.6	>100
P. mirabilis (5)	0.1	≤0.025	3.6	16.5	>100
H. influenzae (20)	0.7	0.06	5.1	30.8	9.8
M. catarrhalis (30)	0.3	0.3	1.8	3.8	2.7
N. gonorrhoeae (3)	≤0.025	≤0.025	0.5	7.9	6.3

[a] ND = Not done.

In a 1989 study by Tomatsu, K. et al., cefdinir demonstrated activity against Gram-negative bacteria producing cefuroxime-inactivating penicillinases. These results are shown on Table 24. However, Gram-negative bacteria producing cefuroxime-inactivating cephalosporinases and oxyiminocephalosporinases are also resistant to cefdinir.

TABLE 24. In Vitro Antibacterial Activity of Cefdinir and Cefuroxime Against β-Lactamase-Producing Strains

Organism	MIC (μg/mL)	
	Cefdinir	Cefuroxime
Penicillinase-Producing		
Escherichia coli ML1410 RGN 823	0.4	6.3
E. coli ML1410 Rms 212	0.8	12.5
E. coli ML1410 RGN 14	0.4	6.3
E. coli ML1410 RGN 238	0.4	12.5
Klebsiella pneumoniae GN69	0.2	3.1
K. pneumoniae GN118	0.2	3.1
Proteus mirabilis N-29	0.2	1.6
P. mirabilis N-29/2	0.1	1.6
Cephalosporinase-Producing		
Escherichia coli GN5482	25	25
E. coli 255	50	>100
E. coli GN206	25	25
Citrobacter freundii GN7391	>100	>100
C. freundii GN346	>100	100
C. freundii GN346/16-10	50	25
Enterobacter cloacae GN7471	>100	>100
E. cloacae 363	>100	>100
E. cloacae 363/1-3	>100	>100
Morganella morganii 1510	50	50
M. morganii 1510/3	3.1	6.3
Serratia marcescens GN10857	>100	>100
Oxyiminocephalosporinase-Producing		
Proteus vulgaris GN7919	25	>100
P. vulgaris GN76/C-1	12.5	>100
P. vulgaris GN76/C-1/1	6.3	>100
P. vulgaris GN76/C-1/3	1.6	25

In a study by Sanders, C.C. et al., a total of 65 hospital isolates of nonfastidious gram-negative bacilli resistant to various β-lactam antibiotics were tested by agar dilution for susceptibility to cefdinir. These included strains possessing well-characterized plasmid- and chromosomally-mediated β-lactamases as well as permeability mutants. Many have been recovered from patients treated unsuccessfully with β-lactam antibiotics. For comparative purposes cefaclor, cefuroxime, cephalexin, cefixime, and amoxicillin/clavulanate were examined in simultaneous tests. As shown in Table 25, cefdinir inhibited 72% of the study strains at concentrations of 1 μg/mL. Only

cefixime showed potency similar to cefdinir by inhibiting 78% of the study strains at concentrations of 1 μg/mL. Strains with cefdinir MICs ≥4 μg/mL were isolates expressing a Class I-cephalosporinase. Table 26 lists these cefdinir resistant isolates.

TABLE 25. Comparative Activity of Cefdinir and Other Oral β-Lactam Antibiotics Against 65 β-Lactam-Resistant Clinical Isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa*

β-Lactam	MIC_{50} μg/mL	MIC_{90} μg/mL	% Inhibited at Breakpoint[a]
Cefdinir	0.25	64	72%
Cefixime	0.25	128	78%
Cefuroxime	8	128	48%
Cefaclor	8	>128	57%
Cephalexin	16	>128	49%
Amoxicillin/Clavulanate	16	64	43%

[a] Breakpoints used were 1 μg/mL for cefdinir and cefixime, 4 μg/mL for cefuroxime, and 8 μg/mL for the remainder.

In a study by Labia, R. et al. Cefdinir was active against the narrow-spectrum, Ambler's class A, plasmid-mediated, β-lactamases TEM-1, TEM-2, and SHV-1, as were cefotaxime, ceftazidime, cefixime and cefuroxime. Cefdinir, as other third-generation cephalosporins, showed some hydrolysis by the novel extended-spectrum β-lactamases (ESBL): TEM-3, TEM-5, SHV-2, MEN-1 and other ESBL. The relationship between the activity of cefdinir against *Enterobacteriaceae* and the type and quantity of β-lactamase produced was thoroughly delineated in another report by Martinez-Beltran, J. et al. It was demonstrated that TEM-3, 4, 5, 6, 7, and SHV-2, 3, 4, 5, β-lactamases increased cefdinir MICs (0.5-16 μg/mL). Hiperproducing constitutive and inducible chromosomal β-lactamase *Enterobacteriaceae* strains showed higher MICs to all β-lactamas (cefdinir, cefixime, cefuroxime, cefaclor, and cefotaxime) investigated.

Briggs, B.M. et al. confirmed the specificity of action of β-lactamases in resistance to cefdinir: Bacteria producing the plasmid-mediated β-lactamases TEM-1, TEM-2, HMS-1, OXA-1, OXA-2, OXA-3, and SHV-1 were all susceptible to cefdinir. *Klebsiella* isolates producing Type III and IV extended-spectrum β-lactamases were less susceptible (MIC = 4 μg/mL), and *Pseudomonas* sp producing Type V CARB-1 were highly resistant (MIC = 16 μg/mL).

As pointed out above, none of the cephalosporins are significantly active against bacteria which express intrinsic, non-β-lactamase-, PBP-mediated, resistance. Data obtained with such bacterial isolates are shown in Table 27.

TABLE 26. Organisms with plasmid and chromosomally-mediated β-lactamases as well as permeability mutants resistant to cefdinir.

Isolates (Enzyme[a])	Cefdinir MIC (μg/mL)
Serratia marcescens 3 (I, I)	32
S. liquefaciens 39 (I, I)	8
Serratia spp TIM24 (I, I, III)[b]	16
Morganella morganii 95 (I, I)	8
Pseudomonas aeruginosa PA038 (I, I)	>128
Enterobacter cloacae VA9 (I, c)	64
Enterobacter cloacae VA10 (I, c, p)	>128
Citrobacter freundii TIM43 (I, c)	128
Citrobacter freundii TIM23 (I, c)	128
Citrobacter freundii TIM13 (I, c)	128
Citrobacter freundii TIM28 (I, c)	64
Citrobacter freundii TIM27 (I, c)	64
E. Coli M289 (SHV-5)	4
E. Coli M233 (SHV-5)	4

[a] Roman numeral indicates Richmond and Sykes Class; I = inducible; c = constitutive; p = porin mutant.
[b] Contained two enzymes, inducible Class I and TEM-1.

TABLE 27. Activity of Cefdinir Against Bacteria Expressing Intrinsic Resistance to β-Lactams

Bacterial Species/ Resistance Type	MIC_{90} (μg/mL)						
	Cefdinir	Cefuroxime	Cefixime	Cefaclor	Cefpodoxime	Cephalexin	Reference[a]
S. aureus / MRSA	64						24
	>128	>128	>128				17
	>16	>32	>4	>32			7
	>128		>128	>128	>128	>128	20
Staphylococci	128						24
Coagulase-Negative	>128	>128	>128				17
Methicillin-Resistant	>128		>128	64	>128	64	20
H. influenzae	2		1				7
Ampicillin-Resistant							
S. pneumoniae	2		2				7
Penicillin-Resistant	8	4	>16	>8	4		66
	8		64	64			20

[a] References are listed numerically on pages 2-26 in volume 47 of the submitted NDA 50-739.

3. Resistance Development During Clinical Trials

The development of resistance during cefdinir clinical studies was evaluated by comparing the disk diffusion and MIC susceptibility results for baseline cultures at study admission with those from subsequent cultures taken either during therapy or post-therapy. Pathogens in this analysis included all those from evaluable patients whose interpretive criteria, using either disk diffusion or MIC methodologies, changed from susceptible or intermediate at study admission to resistant on subsequent culture.

Susceptibility data for the 10 isolates that developed resistance is shown in Table 28. In 2 cases, 2 colony types of the same species were isolated from a single patient, and both colony types developed resistance. Discrepancies between MIC and disk diffusion susceptibility results were seen for 5 pathogens that developed resistance during or after treatment. In 4 cases, the pathogen was resistant by MIC testing, but the disk diffusion interpretation was susceptible. Three of these isolates were from 1 clinical study site. In 1 case, the zone interpretation was resistant, but the MIC interpretation was susceptible. Pathogens were not available for repeat susceptibility testing to confirm these results.

Cefdinir MIC susceptibility data were available for admission and follow-up cultures for 3309

patients, and disk diffusion susceptibility data were available for 3447 patients. Overall resistance development during adult capsule clinical studies was extremely low at 0.2% (7/3309 for MIC data, 6/3447 for disk diffusion data). Six isolates (from 4 patients) were from AECB, 1 was from bronchitis, and 3 (from 2 patients) were from the adult skin structure infection study. No resistance development was seen in pediatric suspension studies.

The organism that most frequently developed resistance was *H. influenzae*, with 4 isolates (from 3 patients). The rate of resistance development for this organism is still low at 0.7% (4/600 isolates). Resistance also developed in 1 strain each of *Serratia proteamaculans*, *K. oxytoca*, *K. pneumoniae*, and 3 strains of *S. aureus* (from 2 patients).

TABLE 31. Development of Resistance During Cefdinir Clinical Studies

Indication	Protocol/Site/ Patient No.	Regimen	Pathogen	Susceptibility Data					
				Initial Isolate			Resistant Isolate		
				Study Day	MIC (μg/mL)	Zone (mm)	Study Day	MIC (μg/mL)	Zone (mm)
AECB	005-001-026	300 mg BID	*Haemophilus influenzae* (β-lactamase pos)	1	0.5 (S)	21 (S)	18	0.5 (S)	10 (R)
	005-014-003	600 mg QD	*H. influenzae* (β-lactamase neg)	1	ND	52 (S)	3	ND	0 (R)
	005-011-054	300 mg BID	*H. influenzae*, Str 1 (β-lactamase neg)	1	ND	24 (S)	22	4 (R)	27 (S)
			H. influenzae, Str 2 (β-lactamase neg)	1	ND	24 (S)	36	8 (R)	24 (S)
	005-011-016	300 mg BID	*Serratia proteamaculans*	1	1 (S)	23 (S)	8	8 (R)	25 (S)
	016-017-008	600 mg QD	*Klebsiella oxytoca*	1	0.125 (S)	28 (S)	3	4 (R)	30 (S)
Bronchitis	016-023-010	600 mg QD	*K. pneumoniae*	1	0.06 (S)	27 (S)	15	ND	11 (R)
Uncomplicated SSSIs	008-019-003	300 mg BID	*Staphylococcus aureus*, Str 1 (OX S)	1	0.25 (S)	27 (S)	15	16 (R)	7 (R)
			S. aureus, Str 2 (OX S)	1	0.25 (S)	27 (S)	24	8 (R)	7 (R)
	008-022-033	300 mg BID	*S. aureus* (OX S)	1	0.25 (S)	30 (S)	16	16 (R)	11 (R)

S = Susceptible; R = Resistant; ND = Not done.

III. PRECLINICAL EFFICACY (*IN VIVO*)

A. Pharmacokinetics and Bioavailability

The information in this section is taken from the NDA studies submitted by the sponsor and have not been reviewed by a Biopharmaceutical Reviewer.

Cefdinir is intended to be used orally in adults and in children for community-acquired lower and upper respiratory tract infections, and for uncomplicated skin and skin structure infections. The targeted lower respiratory diseases include: community-acquired pneumonia, acute exacerbations of chronic bronchitis, and secondary bacterial infections of acute bronchitis. The targeted upper respiratory diseases are acute suppurative otitis media, acute maxillary sinusitis, and pharyngitis/ tonsillitis. This pharmacokinetic overview will focus on the concentrations of cefdinir found in the plasma and the targeted infection sites after oral administration of capsules to adults and oral suspension to children.

Based on pilot plasma concentration studies performed in humans, the recommended cefdinir regimen for the treatment of infections in adults, using a capsule formulation, is either 300 mg twice a day or 600 mg once daily. The equivalent oral doses of suspension in children, ranging in age from 6 months to 12 years, are 7 mg/kg twice a day or 14 mg/kg once daily.

1. Assay Methods

2. Cefdinir Pharmacokinetics

The recommended cefdinir regimen (capsules) for the treatment of infection in adults and adolescents is 300 mg (173 mg/m^2) BID or 600 mg (347 mg/m^2) QD. To define the dose for

Phase 3 pediatric studies that would produce plasma cefdinir concentrations comparable to those observed following 300- and 600-mg capsule doses in adults, adult doses were extrapolated to pediatric doses on a mg/m^2 basis. These doses were then divided by 1.2 to adjust for the higher bioavailability of the suspension. Based upon pharmacokinetic considerations, pediatric doses of 7 to 14 mg/kg cefdinir suspension were recommended to correspond to adult capsule doses of 300 and 600 mg, respectively. The ability of these recommended doses to produce concentrations consistent with 300- and 600-mg doses in adults was confirmed in a pharmacokinetic study in pediatric subjects.

a. Capsules

The pharmacokinetics and dose proportionality of cefdinir after administration of single oral doses of 200, 300, 400, and 600 mg were evaluated. Plasma cefdinir concentrations increased with dose over the 200- to 600-mg dose range (Figure 3). However, plasma concentrations at 600 mg increased less than predicted by a dose-proportional model. Mean maximum cefdinir concentrations were observed approximately 3 hours following all doses and then declined monoexponentially. Mean elimination t½ values of approximately 1.5 hours for all doses indicated cefdinir elimination was not dose dependent (Table 32). Percent of dose recovered in urine as unchanged cefdinir in 24 hours (Ae%) ranged from 12% to 19%, with the lowest recovery following administration of 600 mg. Renal clearance was constant across doses; mean values ranged from 113 to 127 mL/min. The lack of a dose-dependent change in cefdinir elimination suggested that the less than dose-proportional increase in Cmax and AUC values, and reduced Ae% observed at 600 mg were the result of reduced drug absorption.

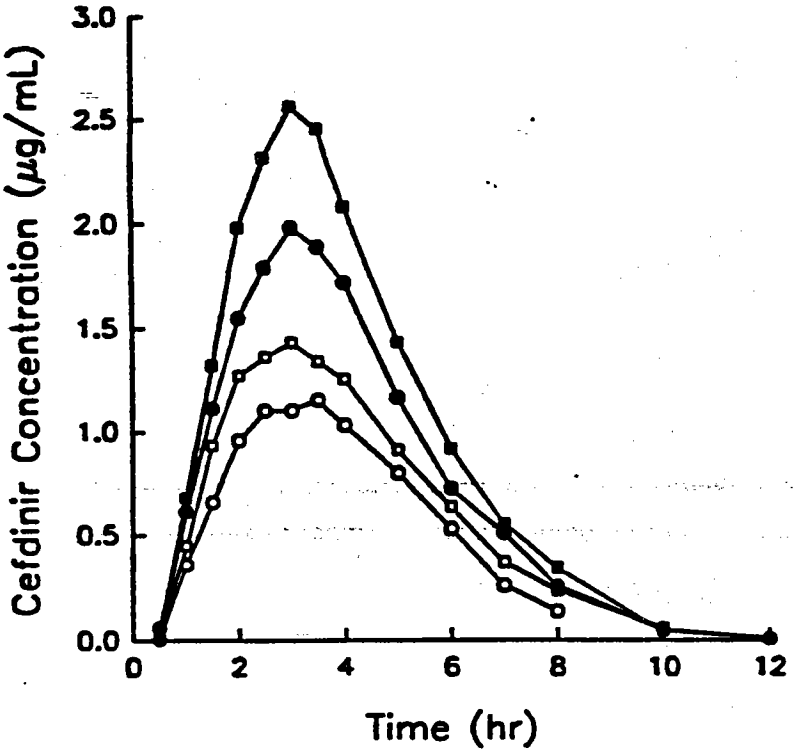


FIGURE 3. Study 983-35: Mean Plasma Cefdinir Concentration-Time Profiles Following Administration of Single 200- (o), 300- (□), 400- (●), and 600-mg (■) Cefdinir Capsule Doses

TABLE 32. Study 983-35: Mean (%RSD) Plasma Cefdinir Pharmacokinetic Parameters Following Administration of Single 200-, 300-, 400-, and 600-mg Cefdinir Capsule Doses (N = 20)

Parameter	200 mg	300 mg	400 mg	600 mg
Cmax, μg/mL	1.29 (33.8)	1.60 (34.5)	2.16 (37.5)	2.87 (35.3)
NCmax, μg/mL	0.0065 (33.8)	0.0053 (34.5)	0.0054 (37.5)	0.0048 (35.3)
tmax, hr	3.1 (30.0)	2.9 (30.5)	3.0 (19.5)	3.0 (21.8)
t½, hr	1.5 (16.2)	1.5 (21.4)	1.4 (17.3)	1.5 (24.6)
λz, hr^{-1}	0.488 (17.3)	0.475 (20.6)	0.496 (17.3)	0.488 (21.7)
AUC(0-∞), μg·hr/mL	5.55 (31.2)	7.05 (30.8)	9.01 (34.9)	11.1 (34.9)
NAUC(0-∞), μg·hr/mL	0.0278 (31.2)	0.0235 (30.8)	0.0225 (34.9)	0.0185 (34.9)
CLr, mL/min	120 (36.3)	114 (47.8)	127 (46.0)	113 (41.4)
Ae%	18.7 (48.2)	14.7 (50.2)	15.7 (47.7)	11.5 (44.8)

%RSD = Relative standard deviation (%).
Cmax = Maximum observed concentration (μg/mL).
NCmax = Maximum observed concentration (μg/mL), normalized to a 200-mg dose.
tmax = Time of Cmax (hr).
t½ = Elimination half-life (hr).
λz = Apparent elimination-rate constant (hr^{-1}).
AUC(0-∞) = Area under the plasma concentration versus time curve from time zero to infinity (μg·hr/mL).
NAUC(0-∞) = Normalized area under the plasma concentration versus time curve from time zero to infinity (μg·hr/mL), normalized to a 200-mg dose.
CLr = Renal clearance (mL/min).
Ae% = Percent (%) of dose excreted unchanged in urine in 24 hours.

In a Phase 1 safety, tolerance, and pharmacokinetic study, subjects received cefdinir as single doses followed by 2 weeks of twice-daily doses up to 600 mg (1200 mg/day). Disposition of cefdinir was similar on Days 1 and 17 at all doses; thus, cefdinir does not accumulate with multiple dosing.

b. Suspension

The pharmacokinetics of cefdinir following administration of single 7- and 14-mg/kg suspension doses were evaluated in children aged 6 months to 2 years (younger) and from 2 to 12 years (older) (Study 983-23). Plasma cefdinir concentrations increased with increasing dose in both age groups (Figure 4). The overall average tmax value was 2.0 hours (Table 33) and mean Cmax and AUC values were similar for both age groups. Plasma cefdinir concentrations generally decreased monoexponentially following attainment of Cmax. Mean plasma elimination t½ values following

administration of both doses were slightly shorter in younger children (1.3 hr) than older children (1.6 hr). Urinary pharmacokinetic values were extremely variable, probably due to incomplete urine collection.

Following similar doses (based on mg/m^2 and accounting for the 120% bioavailability of the pediatric suspension), Cmax and AUC(0-∞) values in children were similar to adults.

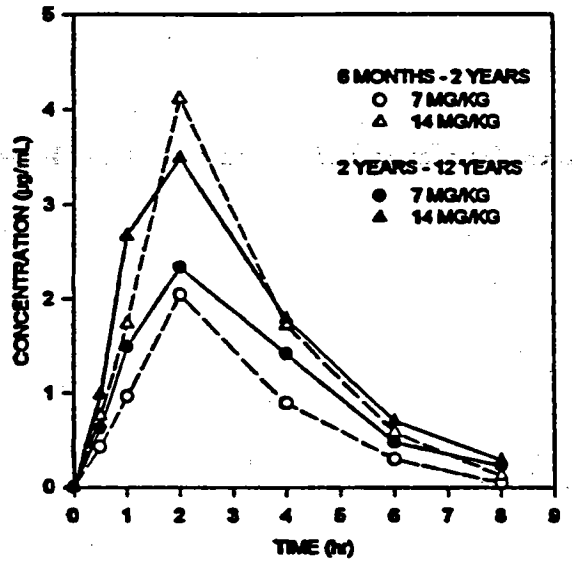


FIGURE 4. Study 983-23: Mean Plasma Cefdinir Concentration-Time Profiles After Administration of Single Suspension Doses of 7 or 14 mg/kg Cefdinir to Subjects Aged 2 to 12 Years and 6 Months to 2 Years

TABLE 33. Study 983-23: Mean (%RSD) Cefdinir Pharmacokinetic Parameter Values After Administration of Single 7- or 14-mg/kg Pediatric Suspension Doses (N = 6)

Age	2 to 12 years		6 months to 2 years	
Dose, mg/kg	7	14	7	14
Parameter				
Cmax, μg/mL	2.56 (25.8)	3.60 (6.4)	2.04 (31.4)	4.11 (20.9)
tmax, hr	2.3 (34.8)	1.7 (29.4)	2.0 (0.0)	2.0 (0.0)
λz, hr^{-1}	0.445 (16.9)	0.458 (17.7)	0.514 (14.8)	0.584 (27.4)
t½, hr	1.6 (12.5)	1.6 (18.8)	1.3 (15.4)	1.3 (23.1)
AUC(0-tldc), μg·hr/mL	9.16 (23.4)	12.9 (12.4)	6.14 (36.2)	12.3 (26.0)
AUC(0-∞), μg·hr/mL	9.83 (22.6)	13.7 (13.9)	6.79 (31.2)	13.0 (27.7)
CLr, mL/min	47.4 (53.0)	23.2 (44.0)	3.33 (109)[a]	22.6 (NA)[b]
Ae%, %	12.7 (33.1)	4.1 (54.2)	2.7 (96.3)[a]	8.7 (NA)[b]

%RSD = Relative standard deviation (%).
Cmax = Maximum observed concentration (μg/mL).
NCmax = Maximum observed concentration (μg/mL), normalized to a 200-mg dose.
tmax = Time of Cmax (hr).
λz = Apparent elimination-rate constant (hr^{-1}).
t½ = Elimination half-life (hr).
AUC(0-tldc) = Area under the plasma concentration versus time curve from time zero to last detectable concentration (μg·hr/mL).
AUC(0-∞) = Area under the plasma concentration versus time curve from time zero to infinity (μg·hr/mL).
CLr = Renal clearance (mL/min).
Ae% = Percent (%) of dose excreted unchanged in urine in 24 hours.
[a] N = 3.
[b] N = 1.

3. Inter- and Intrasubject Variability

There was notable variation in pharmacokinetic parameter values as %RSD values associated with most mean pharmacokinetic parameter values ranged from 30% to 50%. Intrasubject variation of Cmax and AUC(0-∞) values was 27%.

4. Volume of Distribution, Protein Binding, and Tissue Penetration

The volume of distribution (Vd_{area}) of cefdinir was estimated to be 0.35 L/kg. This value is about 50% greater than extracellular fluid volume.

Cefdinir is approximately 60% to 70% bound in serum and plasma; protein binding is neither age- nor concentration-dependent.

Partitioning of radioactivity into erythrocytes is minimal; mean erythrocyte-to-plasma ratios range from 0.17 to 0.23.

The penetration of cefdinir into suction-induced skin blisters was characterized in healthy adult subjects who received single, oral capsule doses of 200, 300, 400, and 600 mg. The results are given in Table 34. Mean blister fluid concentrations increased proportionately to increases in plasma cefdinir concentrations. Overall mean blister fluid Cmax value was 48% and AUC(0-∞) was 91% of plasma values.

TABLE 34. Study 983-25: Mean (%RSD) Plasma and Blister Fluid Cefdinir Pharmacokinetic Parameters Following Administration of Single 200-, 300-, 400-, and 600-mg Cefdinir Capsule Doses (N = 16)

Parameter	200 mg	300 mg	400 mg	600 mg
Plasma Parameter Values				
Cmax, μg/mL	1.00 (25.4)	1.55 (37.5)	2.15 (52.9)	2.36 (28.4)
tmax, hr	3.3 (19.0)	3.2 (18.9)	3.0 (21.1)	3.3 (23.2)
AUC(0-∞), μg·hr/mL	4.15 (27.9)	6.61 (41.6)	8.95 (52.3)	9.99 (34.3)
t½, hr	1.71 (17.3)	1.64 (9.1)	1.66 (19.3)	1.75 (23.7)
Blister Fluid Parameter Values				
Cmax, μg/mL	0.558 (27.5)	0.674 (37.7)	0.890 (40.4)	1.091 (34.5)
tmax, hr	4.8 (21.8)	4.9 (18.2)	4.8 (20.4)	4.7 (24.3)
AUC(0-∞), μg·hr/mL	4.36 (25.0)	5.51 (41.1)	7.24 (45.2)	8.99 (34.8)
t½, hr	3.26 (21.1)	3.69 (21.0)	3.7 (23.1)	3.72 (19.6)
Blister Fluid to Plasma Ratio				
Cmax	0.565 (20.5)	0.448 (27.5)	0.442 (26.3)	0.473 (28.7)
AUC(0-∞)	1.06 (15.3)	0.849 (16.3)	0.829 (13.3)	0.913 (21.9)

%RSD = Relative standard deviation (%).
Cmax = Maximum observed concentration (μg/mL).
tmax = Time of Cmax (hr).
AUC(0-∞) = Area under the plasma concentration versus time curve from time zero to infinity (μg·hr/mL).
t½ = Elimination half-life (hr).

Cefdinir concentrations were measured in tonsil tissue, sinus tissue, bronchial mucosa, epithelial lining fluid, and middle ear fluid. These determinations are summarized in Table 35.

TABLE 35. Mean (Range) Plasma and Fluid/Tissue Cefdinir Concentrations and Fluid/Tissue to Plasma Ratios Following Administration of Single Cefdinir Doses

Fluid/Tissue	Dose (mg)	N	Time of Sample Collection (hr postdose)	Plasma Concentration (μg/mL)	Fluid/Tissue Concentration (μg/mL or μg/g)	Fluid/Tissue-to-Plasma Ratio
Tonsil	300	6	4	1.13 (0.6-2.0)	0.28 (0.22-0.46)	0.27 (0.16-0.43)
	600	6	4	2.17 (1.1-3.4)	0.44 (0.22-0.80)	0.21 (0.14-0.29)
Sinus	300	6	4	0.97 (0.7-1.4)	0.12 (0.0-0.46)[a]	0.12 (0.0-0.42)[a]
	600	6	4	2.27 (0.8-3.5)	0.46 (0.0-2.0)[b]	0.20 (0.0-0.57)[b]
Bronchial Mucosa	300	8	4	2.79 (1.40-8.00)	0.77 (0-1.33)	0.37 (0 - 0.67)
	600	8	4	4.46 (3.05-6.40)	1.08 (0-1.92)	0.25 (0-0.35)
Epithelial Lining Fluid	300	8	4	2.79 (1.40-8.00)	0.97 (0-4.73)	0.65 (0 - 3.26)
	600	8	4	4.46 (3.05-6.40)	0.38 (0-0.59)	0.09 (0-0.14)
Middle Ear Effusion	7 mg/kg	6	3	1.96 (0.80-3.22)	0.23 (0.0-0.94)	0.10 (0.0-0.40)
	14 mg/kg	8	3	3.37 (0.89-5.54)	0.63 (0.0-1.42)	0.20 (0.0-0.35)

[a] 11 samples from 6 subjects
[b] 10 samples from 6 subjects

Penetration of cefdinir into tonsil tissue was investigated in adults undergoing elective tonsillectomy. Mean tonsil tissue concentrations 4 hours after administration of single 300- and 600-mg doses were 0.28 (±0.09) and 0.44 (±0.24) μg/g, respectively. Mean tonsil tissue concentrations were 24% (±8) of corresponding plasma concentrations.

Penetration of cefdinir into sinus tissue was investigated in adults undergoing elective surgery on the maxillary and ethmoid tissues. Mean sinus tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.12 (±0.18) and 0.46 (±0.66) μg/g, respectively. Mean sinus tissue concentrations were 16% (±20) of corresponding plasma concentrations.

Penetration of cefdinir into bronchial mucosa and epithelial lining fluid was evaluated in adults undergoing diagnostic fiberoptic bronchoscopy. Mean bronchial mucosa cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.77 (±0.39) and 1.08 (±0.63) μg/mL, respectively. Mean lung tissue concentrations were 31% (±18) of corresponding plasma

Interactions between cefdinir and several drugs were observed. As with other β-lactam antibiotics, probenecid inhibited renal tubular secretion of cefdinir, reducing cefdinir clearance and prolonging its t½.

Cefdinir Cmax was reduced 38% and AUC(0-∞) was reduced 44% when coadministered with Maalox TC®. There was no significant effect on cefdinir pharmacokinetics if administered 2 hours before or after the antacid.

Concomitant administration of cefdinir with iron reduced cefdinir bioavailability. The extent of the reduction was dependent on the dose of coadministered iron, being greatest (80%) in the presence of a therapeutic iron supplement (60 mg elemental iron). The effect was reduced when cefdinir and iron doses were separated by 2 hours. Therefore, it is recommended that if iron supplements are required during cefdinir therapy, cefdinir should be taken at least 2 hours after the iron supplement. The exception is iron-fortified infant formula, which did not have a clinically significant impact on cefdinir bioavailability.

7. Special Populations

Because cefdinir elimination is mediated predominantly by renal excretion, reduced renal function alters cefdinir pharmacokinetics. When cefdinir was administered to subjects with impaired renal function, cefdinir Cmax, AUC, and t½ were all elevated. It is recommended that cefdinir dosage be adjusted only in patients with intrinsic renal dysfunction (creatinine clearance values <30 mL/min), who should receive a 300-mg cefdinir dose once daily. Cefdinir is effectively removed from the body by dialysis, necessitating a further dosage adjustment. In patients on chronic hemodialysis treatment, the recommended initial cefdinir regimen is 300 mg every other day; at the conclusion of each hemodialysis session patients should receive 300-mg dose of cefdinir. Subsequent doses should be administered every other day.

Because cefdinir is not appreciably metabolized, studies were not performed in subjects with hepatic impairment.

Cefdinir Cmax, AUC, and t½ were elevated in subjects 65 years or older compared to subjects 18 to 30 years of age. This was attributable to an age-related decline in renal function. Thus, a dosage adjustment in elderly patients is not required unless they have intrinsic renal dysfunction.

Gender and race had no significant impact on cefdinir pharmacokinetics.

8. Pharmacokinetics in Patients

Cefdinir pharmacokinetics in patients were similar to those in healthy subjects, according to meta-analysis of 4-hour cefdinir concentration data derived from 158 patients from clinical trials with the following infections: pneumonia, acute maxillary sinusitis, pharyngitis/tonsillitis, skin and skin structure infections, or secondary infections of acute bronchitis. Statistical comparisons were made with data from 154 healthy subjects. These results are displayed in Figure 5. Pharmacokinetic profiles from a study in patients with lower respiratory tract infections were similar to those in healthy subjects.

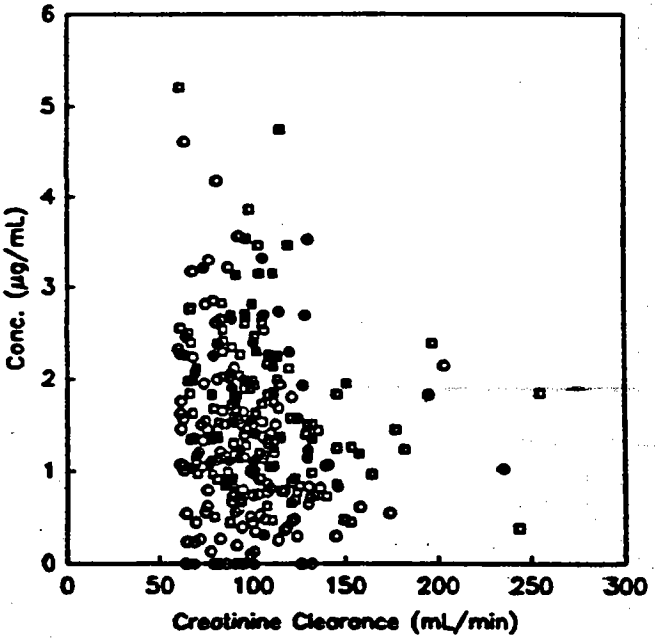


FIGURE 5. Plasma Cefdinir Concentration at 4 Hours Postdose Versus Creatinine Clearance Values Following Administration of Cefdinir to Adult Patients and Subjects. Circles represent patients, squares represent healthy subjects; open symbols represent 300-mg doses, filled symbols represent 600-mg doses.

B. Influence of Cefdinir on the Intestinal Bacterial Flora in Humans After Oral Dosing

The data obtained in a clinical study in 7 children indicate that cefdinir has a relatively small

influence on the intestinal bacterial flora.[99] In this pediatric study, 7 children with infections (3 boys and 4 girls) were treated orally with 3.0 to 3.7 mg/kg per day of cefdinir fine granules 3 times a day for 4 to 14 days. The ages of the children ranged from 6 months through 12 years 7 months, and their weight distribution was 5.5 to 29.2 kg. During drug administration, some changes were observed in the pattern of the fecal bacterial flora between subjects. Although *Enterobacteriaceae* and total anaerobes were markedly decreased in 2 cases, total counts of aerobes were unchanged in these individuals. In other cases, predominant aerobes excepting enterococci and anaerobes hardly varied. There was no case in which glucose nonfermenting gram-negative rods or fungi became predominant species for any length of time. Although *C. difficile* and *C. difficile* D-1 antigens were detected in 1 and 4 cases, respectively, no relationships were found between the number of *C. difficile* and the characteristics of the feces.

IV. CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

A. Clinical Laboratory Susceptibility Test Methods

The information summarized in this section is to define the standardized methods to be used by clinical microbiology laboratories to determine the susceptibility of clinical isolates to cefdinir.

1. Susceptibility Interpretive Breakpoints in Dilution Tests

A mean peak plasma concentration (Cmax) of 2.87 μg/mL was obtained from 20 healthy, fasted subjects given a single 600-mg oral dose of cefdinir.[6] A dose of 300 mg provided a mean Cmax of 1.6 μg/mL. The plasma half-life was 1.5 hours for both the 300- and 600-mg doses.

Based on these human pharmacokinetic data, and the use of a 300-mg twice daily dose or a 600-mg once daily dose of cefdinir being used in clinical evaluations, Jones and colleagues suggested that the following tentative susceptibility criteria be applied in the clinical trials[21,84-87].

For nonfastidious bacteria (on cation-adjusted Mueller-Hinton) and *H. influenzae* (on *Haemophilus* Test Medium):

Susceptible	MIC ≤1 μg/mL
Intermediate	MIC = 2 μg/mL
Resistant	MIC ≥4 μg/mL

For *N. gonorrhoeae* on GC agar medium:

Susceptible	MIC ≤ 0.25 μg/mL

This is the same breakpoint applied to cefixime, a structurally similar compound. Because all 100 strains tested were susceptible to 0.015 μg/mL of cefdinir, more definitive breakpoints must await the emergence of cefdinir-resistant isolates.

For *S. pneumoniae*:

Susceptible	MIC ≤0.5 μg/mL
Intermediate	MIC 1.0 μg/mL
Resistant	MIC ≥2 μg/mL

These breakpoints were guided by data from extensive tests utilizing isolates with varying susceptibilities to penicillin.[62] The selected breakpoints separated 2 populations of pneumococci on the basis of penicillin resistance. With these breakpoints, all 64 penicillin-resistant strains tested were resistant to cefdinir and all penicillin-susceptible strains were susceptible to cefdinir. Of the 87 strains with intermediate susceptibility to penicillin, 68 (78%) were susceptible to cefdinir, 5 (6%) were intermediate, and 14 (16%) were resistant to cefdinir.

2. Susceptibility Interpretive Criteria in Disk Diffusion Tests

Disk mass ranging studies with cefdinir 5-, 10-, 20-, 30-, and 50-μg disks showed that a 5- or 10-μg disk zone would be the best to correlate with projected MIC susceptible breakpoints of ≤1 or ≤2 μg/mL.[85] These preliminary tests revealed no very major errors (false susceptible zone diameter) and only 1 major error (false resistant zone diameter) when 5-μg disks were applied to the evaluation of 20 strains of enteric bacteria (14 species), 9 nonenteric gram-negative bacilli (5 species), and 20 strains of gram-positive cocci (4 species).

To define tentative disk susceptibility guidelines for clinical trials, Jones utilized 100 bacterial

isolates to investigate the correlation of MIC and disk zone diameters.[83] Microorganisms investigated included 19 strains of *E. coli*, 9 strains of *C. diversus*, 10 strains of *Y. enterocolitica*, 20 strains of *K. pneumoniae*, 19 strains of *C. freundii*, and 19 strains of *S. aureus*. Based on regression and error rate bounded analyses of the scattergrams obtained by plotting MIC and inhibition zone diameters obtained with 5-μg disks, the following interpretive criteria were recommended for nonfastidious bacteria:

Susceptible	≥20 mm (MIC equivalent ≤1 μg/mL)
Intermediate	17 to 19 mm (MIC equivalent = 2 μg/mL)
Resistant	≤16 mm (MIC equivalent ≥4 μg/mL)

Jones stated that, application of these criteria would produce no more than 1% very major (false-susceptible) errors if methicillin-resistant staphylococci are considered resistant to cefdinir. The major and minor combined errors should be no greater than 5%.

Disk diffusion breakpoints for these rapidly growing bacteria were confirmed by Jones, R.N. et al. in a more extensive analysis.[84] MICs and zones were obtained with 403 isolates divided into the following categories: 239 strains of the family *Enterobacteriaceae* (23 species), 77 strains of staphylococci (25 oxacillin-resistant), 45 strains of other gram-positive species, 22 strains of *P. aeruginosa*, 10 strains of *S. maltophilia*, and 10 strains of *Acinetobacter* spp. The scattergram derived from these comparisons were subjected to regression and error rate bounded analyses. The investigators concluded that the preferred and proposed interpretive criteria were zone diameters of ≥20 mm for susceptible and ≤16 mm for resistant, values identical to the preliminary parameters listed above. Using these breakpoints, there were 0.6% very major errors (false-susceptible), 0.6% major errors (false-resistant), and 6.4% minor errors. However, to achieve this correlation required the exclusion of data obtained with 43 *Enterobacter* isolates. This species was responsible for 7 of the 9 false-susceptible breakpoints associated with enteric species producing Type I (Richmond-Sykes) cephalosporinase. The authors cautioned that the use of these criteria will miscategorise 20-30% of cefdinir-resistant *Enterobacter* spp. as minimally susceptible. Similar problems have been observed with other oral cephalosporins such as loracarbef and cefetamet with disk tests indicating false susceptibility to several enteric bacilli such as *M. morganii*, *Enterobacter* spp., and *P. stuartii*, as well as oxacillin-resistant staphylococci.

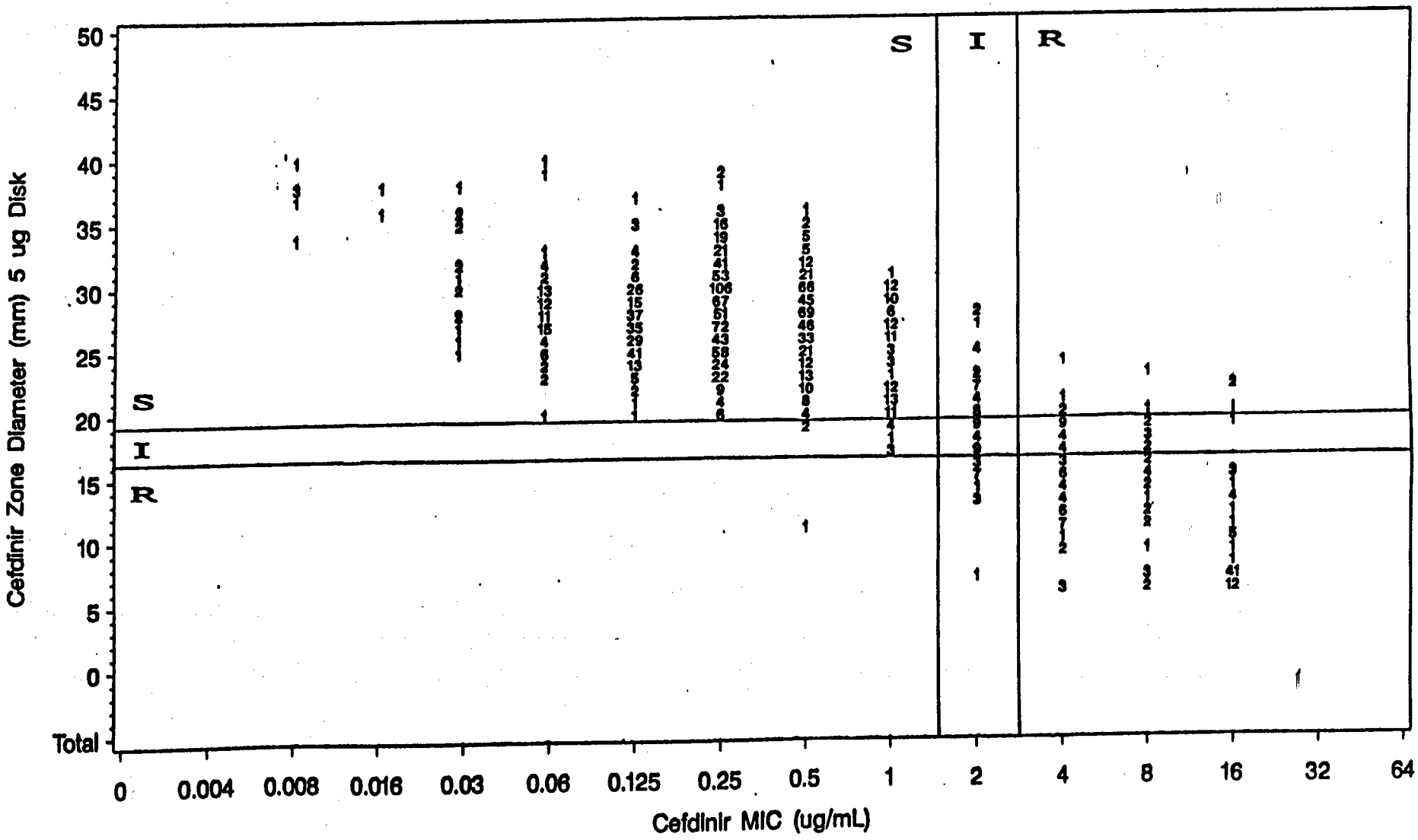
An additional study by Biedenbach, D.J. and Jones, R.N., revealed an unacceptably high very major and minor error rates when cefdinir disks were tested against 100 strains of *Proteus vulgaris* and *Providencia* species.[85] The results indicated that the suggested disk diffusion

breakpoints for cefdinir exceeded acceptable interpretive error rates, with very major (false-susceptible) error of 5% and a minor error of 15%. The authors suggested to have a warning similar to that for loracarbef in the NCCLS table footnotes addressing this problem (footnotes j. and m. in table 2 of M2-A6).
In a study by Biedenbach. D.J., et al.[89], analysis relating zone diameters to MICs against *Morganella morganii* revealed no major error and a 1% minor error.

A scattergram using all US pathogens (other than *Haemophilus* spp. or *Streptococcus* spp.) tested by central laboratories during cefdinir clinical trials is shown in Figure 6. These results confirm the disk diffusion breakpoints proposed by Jones. Very major, major, and minor error rates are 0.5, 0.06 and 4.8% respectively. All organisms with interpretive errors are listed in Table 36. The majority of errors were caused by *Enterobacter* spp. and *Enterococcus* spp. When these organisms are eliminated, very major, major, and minor error rates are 0.06, 0.06, and 1.7%.

FIGURE 6 . Cefdini. .IC vs. Zone Diameter

All Pathogens Other Than *Haemophilus* spp. and *Streptococcus* spp. From US Clinical Sites



Very Major Errors=0.5% (9/1640)
OR 5.7% (9/159 Resistant Orgs.)

Major Errors=0.06% (1/1640)
OR 0.07% (1/1416 Susceptible Orgs.)

Minor Errors=4.8% (78/1640)

TABLE 36. Organisms Causing Interpretive Errors
(Pathogens Other Than *Haemophilus* spp. and *Streptococcus* spp.)

Pathogen	No. Tested	No. Very Major Errors	No. Major Errors	No. Minor Errors
Acinetobacter anitratus	33			11
A. lwoffii	24		1	6
Enterobacter aerogenes	31	1		9
E. cloacae	48	4		13
E. intermedius	1			1
Enterococcus durans	2			1
E. faecalis	63	3		26
E. faecium	5			1
Klebsiella pneumoniae	103			1
Pantoea agglomerans	33			1
Serratia marcescens	14	1		4
Staphylococcus aureus	896			2
S. simulans	1			1
Vibrio parahaemolyticus	1			1
Other Pathogens	385			
Total	**1640**	**9**	**1**	**78**

Similar tests, performed with fastidious bacterial species, have led to the proposed disk diffusion susceptibility guidelines shown in Table 37:[82,86,87]

TABLE 37. Proposed Interpretive Criteria for Fastidious Organisms

Species	Susceptible	Intermediate	Resistant
H. influenzae	≥20[a] (≤1)[b]	17-19 (2)	≤16 (≥4)
N. gonorrhoeae	≥31 (≤0.25)	None	None
S. pneumoniae	≥23 (≤0.5)	20-22 (1)	≤19 (≥2)

[a] Zone diameter in mm

[b] Equivalent dilution breakpoint in μg/mL

Disk diffusion susceptibility guidelines for *H. influenzae* were obtained by the investigation of 100

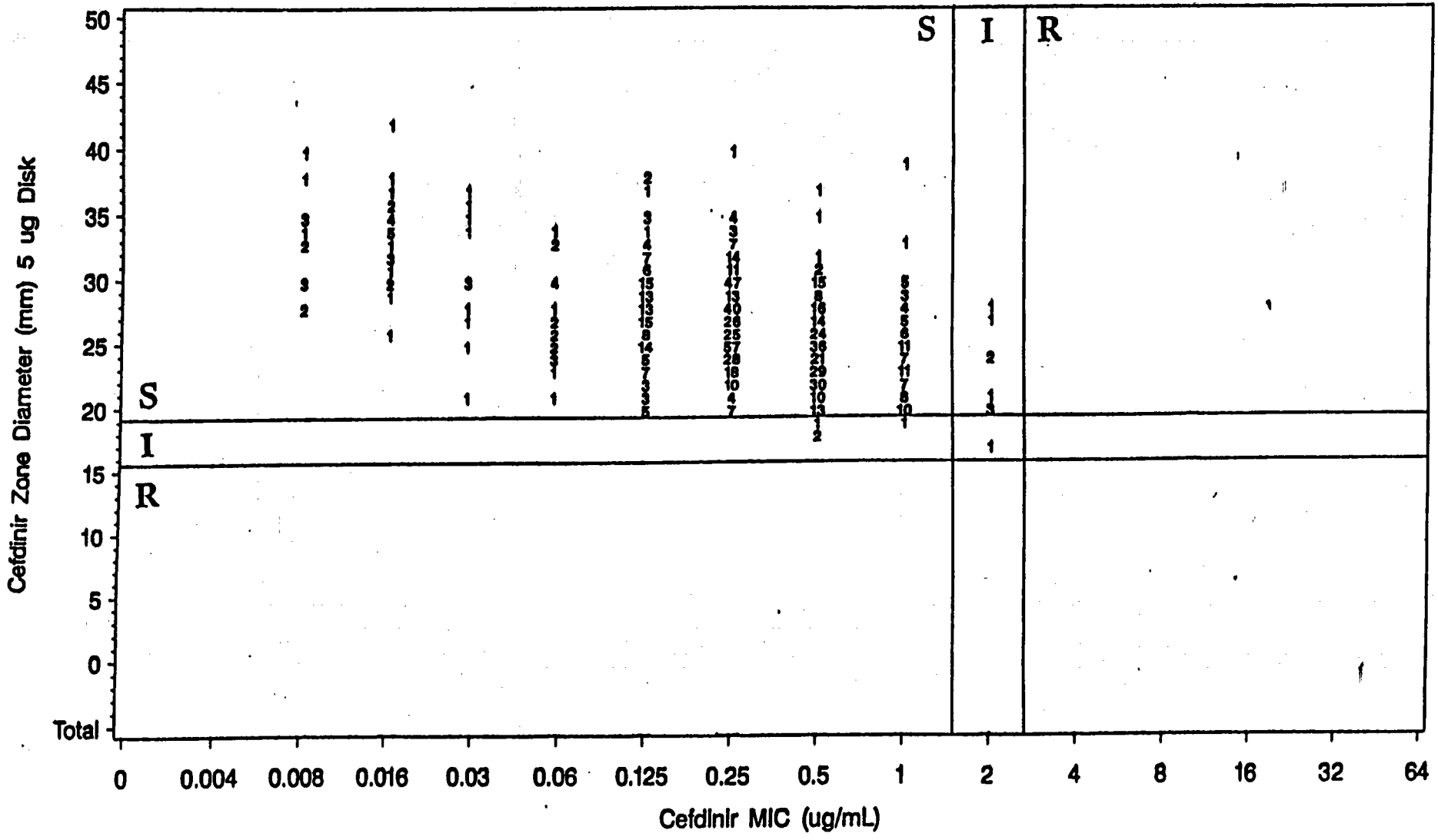
clinical strains in MIC and zone diameter susceptibility tests employing *Haemophilus* test medium.[86] Among the 100 isolates were 26 β-lactamase producing strains, 16 β-lactamase-negative ampicillin-resistant strains (BLNAR), and 58 ampicillin-susceptible strains. These investigators concluded that the proposed breakpoints that have been applied to rapidly growing bacteria were also applicable to *H. influenzae*. Using the above guidelines, there were 1% very major and 6% minor interpretive errors. There were no major errors. All errors were attributed to β-lactamase-negative ampicillin-resistant (BLNAR) strains.

These proposed breakpoints were confirmed by clinical trial data. The scattergram generated from all *Haemophilus* spp. from clinical trials is shown in Figure 7. The very major, major and minor error rates for all *Haemophilus* spp. combined were 0, 0, and 1.5% (12/819), and were 0, 0, and 1.7% (6/356) when considering only *H. influenzae*. None of the 6 minor errors were caused by BLNAR strains.

In a study by Barrett and Jones [87] the susceptibility testing interpretive criteria for cefdinir against 100 *N. gonorrhoeae* isolates was investigated on GC agar medium. Because all strains were susceptible to 0.015 μg/mL of cefdinir, the recommended susceptible interpretive criteria were as follows: for a 5-μg disk, ≥31 mm (MIC correlate, ≤ 0.25 μg/mL). This is the same breakpoint applied to cefixime, a structurally similar compound.

Disk diffusion breakpoints for *Streptococcus pneumoniae* were derived from studies involving a challenge set of 350 clinical isolates.[62] These included 199 penicillin-susceptible isolates (penicillin MIC ≤0.06 μg/mL), 87 with intermediate susceptibility to penicillin (MIC 0.125 to 1.0 μg/mL), and 64 penicillin-resistant strains (MIC ≥2 μg/mL). For definition of disk diffusion breakpoints, MIC breakpoints of ≤0.5 μg/mL for susceptible, 1.0 μg/mL for intermediate, and ≥2 μg/mL for resistant were used. These breakpoints clearly separate 2 populations of pneumococci. Furthermore, with these breakpoints all 64 penicillin-resistant strains were resistant to cefdinir, and all penicillin-susceptible strains were susceptible to cefdinir. Of the 87 strains with intermediate susceptibility to penicillin, 68 (78%) were susceptible to cefdinir, 5 (6%) were intermediate, and 14 (16%) were resistant to cefdinir. Using regression analysis, the susceptible zone diameter breakpoint is calculated to be 23.2 mm, rounded off to 23 mm. With a resistant breakpoint of ≤19 mm and an intermediate range of 20 to 22 mm, there were only 2 false-susceptible disk tests (very major error rate of 0.6% or 2.6% of the 78 resistant strains), no major errors (false resistant disk tests), and 10 minor errors.

FIGURE 7. Cefdinir MIC vs. Zone Diameter For *Haemophilus* spp. (Isolates From Clinical Trials)



Very Major Errors=0% **Major Errors=0%** **Minor Errors=1.5% (12/819)**

(Minor errors considering only *H. influenzae* = 6/356=1.7%)

3. Comparison of MIC Broth and MIC Agar Dilution Assay Methods

In a study by Garcia, F.S, cefdinir susceptibilities were determined by agar dilution and microbroth dilution methods against 122 test strains of bacteria. The species tested were *A. anitratus, E. aerogenes, E. coli, E. cloacae, E. faecalis, S. aureus* (methicillin-susceptible and -resistant), *K. oxytoca, K. pneumoniae, M. catarrhalis, M. morganii, P. mirabilis, P. aeruginosa, S. epidermidis* (methicillin-susceptible), and *S. marcescens.* There was 90.9% agreement (±1 dilution in MIC) among the results from the 2 methods. In 78 of the cases, the MICs were identical; the microbroth MIC was one-half the agar dilution MIC in 22 and twice as high in 11. In only 2 cases were >4-fold shifts encountered. Discordant results were seen most often with *E. faecalis*, with agar dilution MICs at least 4-fold higher than microbroth MICs for 5 of the 10 strains tested.

4. Cross-Resistance With Penicillin for Streptococci

Cefdinir MICs for *S. pneumoniae* increase with increasing penicillin MICs. A study conducted at Clinical Microbiology Institute used 350 strains of *S. pneumoniae* including 199 penicillin-susceptible, 87 penicillin-intermediate and 64 penicillin-resistant strains to compare cefdinir and penicillin MICs. In this study by Fuchs, et al., cefdinir clearly showed cross-resistance with penicillin when testing *S. pneumoniae.*

A study was conducted by Barry, A. et al. to assess the cross-resistance of cefdinir and penicillin when testing *Streptococcus* spp. other than *S. pneumoniae.* Four laboratories participated in testing 484 well characterized stock cultures of streptococci, each testing a different group of 121 species. Data from the four centers were combined for analysis but data with *S. pneumoniae,* viridans streptococci and beta haemolytic streptococci were analyzed separately to determine the practical utility of cefdinir disk tests. The author conclueds that cefdinire disk tests are usually not neede for testing streptococci since penicillin-susceptibility can be assumed to correlate with cefdinir susceptibility. Disk diffusion tests with 10 unit penicillin disks appear to be somwhat more reliable than those 5-µg cefdinir disks when testing pneumococci. For beta haemolytic streptococci, a 5-µg cefdinir disk is preferred over a penicillin disk. For viridans streptococci, a dilution test is prefered over either disk.

5. Cross-Resistance With Other Cephalosporins

The total number of strains which tested intermediate or resistant to each of the oral cephalosporins used in the >5000 isolate study are shown in Table 38(organisms that were not speciated and *Pseudomonas* spp. and *Enterococcus* spp. were deleted due to space considerations). Also, a cross-resistance plot of cefdinir vs. cephalexin from pathogens isolated from clinical trials (adult and pediatric skin infections) is shown in Figure 8. There is a general agreement of resistance, but a class disk cannot be used to determine the susceptibility to cefdinir.

TABLE 38. Cross-Resistance of [illegible]ir With Other Oral Cephalosporins

	Number of Intermediate and Resistant Strains					
Organism	No. Tested	Cefdinir	Cefaclor	Cefuroxime	Cefadroxil	Cefixime
Gram-Negative Strains						
Acinetobacter spp.	74	57	68	70	70	74
A. lwoffii	10	2	1	5	3	6
Citrobacter diversus	46	6	11	14	13	5
C. freundii	98	53	89	39	88	62
Enterobacter aerogenes	161	87	151	84	148	74
E. agglomerans	18	4	3	3	4	2
E. cloacae	322	248	312	241	296	167
Escherichia coli	1029	31	82	103	226	41
Klebsiella oxytoca	95	10	8	4	7	4
K. pneumoniae	391	8	8	55	70	8
Morganella morganii	69	64	62	4	61	16
Proteus mirabilis	194	6	10	10	132	6
P. vulgaris	24	17	10	18	20	0
Providencia rettgeri	13	3	12	4	13	1
Serratia marcescens	105	104	104	101	102	29
Total - Gram-Negative Strains	2649	700	931	755	1253	495

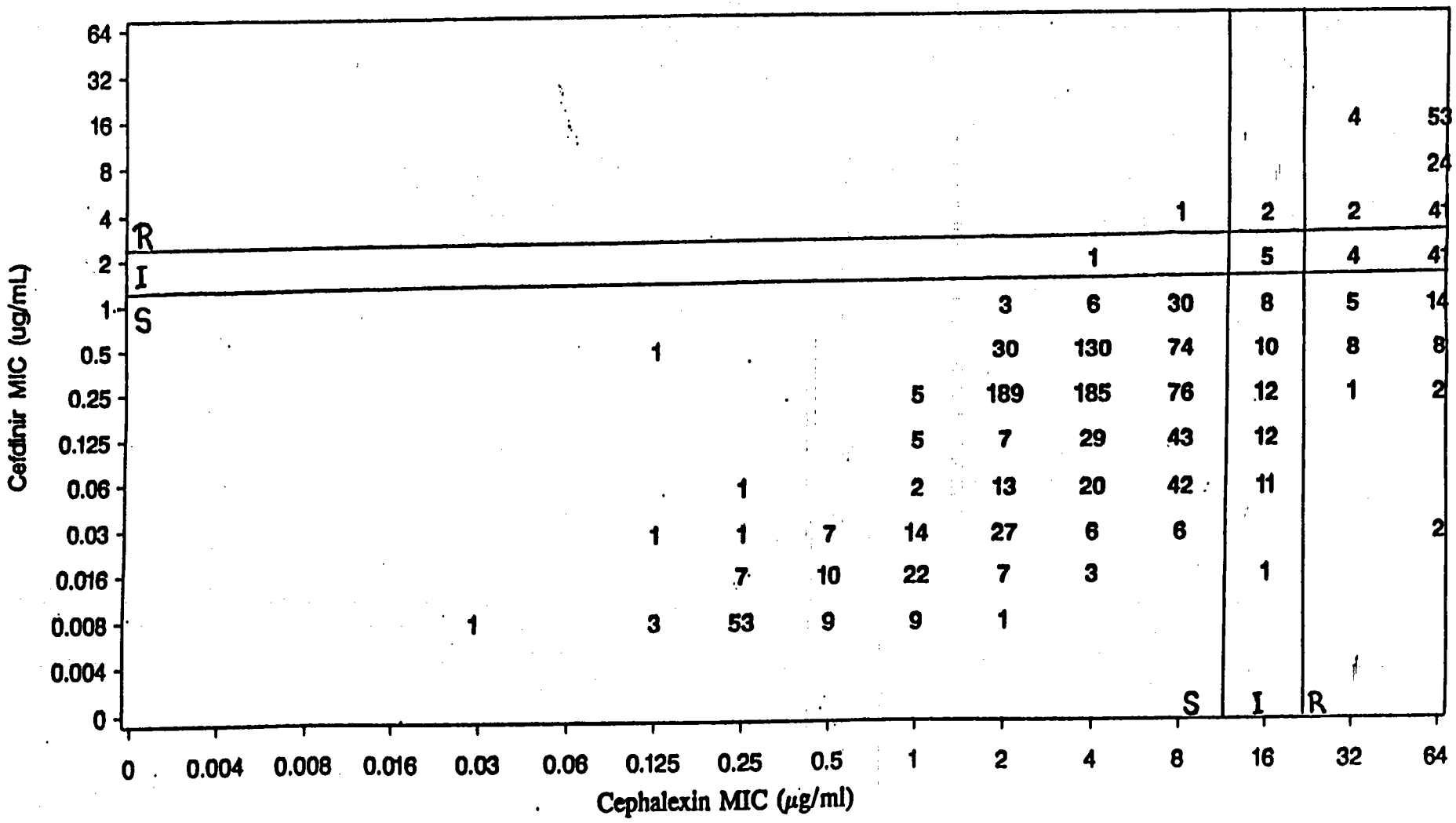
(Continued on next page)

TABLE 38. (Continued)

Organism	No. Tested	Number of Intermediate and Resistant Strains				
		Cefdinir	Cefaclor	Cefuroxime	Cefadroxil	Cefixime
Gram-Positive Strains[a]						
Staphylococcus aureus	794	95	135	71	103	788
S. epidermidis	87	33	36	26	44	86
S. haemolyticus	12	4	5	5	6	12
Staphylococcus spp.	24	1	2	1	1	20
Coag-negative *Staphylococcus spp.*	419	122	142	88	155	385
Streptococcus, Gp. B	52	0	0	0	0	2
Total - Gram-Positive Strains	1388	255	320	191	309	1293

[a] includes some methicillin-resistant strains of staphylococci

FIGURE 8. Cross-Resistance of Cefdinir MIC vs. Cephalexin MIC
(Data from Cefdinir Skin Infections Clinical Trials)



Total Number Tested = 1350
Number Susceptible to Cefdinir and Resistant to Cephalexin=40
Number Susceptible to Cefdinir and Intermediate to Cephalexin=54

6. Quality Control Studies

a. Quality Control Ranges for Dilution Susceptibility Tests

Based on the data discussed in this section, the ranges for the quality control organisms listed in Table 39 are proposed for dilution susceptibility testing with cefdinir.

TABLE 39. Quality Control Ranges for Dilution Tests (NCCLS-Approved)

Organism	Quality Control Ranges (μg/mL)
E. coli ATCC 25922	0.12 to 0.5
S. aureus ATCC 29213	0.12 to 0.5
H. influenzae ATCC 49766	0.12 to 0.5
S. pneumoniae ATCC 49619	0.03 to 0.25

Microbroth dilution MIC quality control ranges were determined for nonfastidious bacteria in cation-adjusted Mueller-Hinton broth (CAMHB). The test organisms were: *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, and *P. aeruginosa* ATCC 27853. Unique test lots of trays were prepared by each of the 6 participating medical centers, and a common lot of trays was prepared for all by the coordinating laboratory as an interlaboratory control. Five tests were run at each center with the common lot, and 20 tests were performed with each of the 6 unique lots. The results of these tests are summarized in Table 40. Based on these data, the above MIC ranges, as presented in Table 39 are proposed for *E. coli* ATCC 25922 and *S. aureus* ATCC 29213. Due to the high MICs obtained, *E. faecalis* ATCC 29212 and *P. aeruginosa* 27853 are not recommended for cefdinir quality control testing. In addition, cefdinir is not intended to treat infections caused by these organisms.

MIC quality control guidelines for *Haemophilus influenzae* ATCC 49766 were determined by microbroth dilution in Haemophilus Test Medium (HTM). A common lot of trays utilizing 8 different lots of HTM broths were prepared and distributed to 6 different laboratories. One hundred twenty MICs were generated at each laboratory. Based on the results shown in Table 40, a range of 0.12 to 0.5 μg/mL is being proposed by the sponsor.

Testing with *H. influenzae* ATCC 49247 was also conducted. As shown in Table 40, results with this strain are not as reproducible when compared with results from *H. influenzae* ATCC 49766. Variable results are also seen with several other cephalosporins with this strain. Therefore, *H. influenzae* ATCC 49247 was not recommended by the sponsor for cefdinir quality control testing.

Agar dilution MICs were performed (Table 40) with cefdinir against *N. gonorrhoeae* ATCC 49226 in a standard multilaboratory study protocol to define quality control guidelines using GC agar from 3 different manufacturers. The common-lot results revealed a technical variation by 1 participating laboratory; that laboratory's data were therefore excluded from unique-lot analysis. The results support a quality control MIC range of 0.008 to 0.03 μg/mL when cefdinir is tested against this organism in agar dilution susceptibility tests.

MIC quality control guidelines for *Streptococcus pneumoniae* ATCC 49619 were determined by microbroth dilution in CAMHB + LHB. All values fell into the MIC range of 0.06 to 0.25 μg/mL, with an apparent bimodal distribution between 0.06 and 0.12 μg/mL. Therefore, a 4-dilution range of 0.03 to 0.25 μg/mL is proposed by the sponsor.

TABLE 40. Quality Control Results for Dilution Tests

Organism (Proposed Range, μg/mL)	Test Medium	MIC (μg/mL)	No. of Occurrences at MIC	
			Unique Lot	Common Lot
E. coli ATCC 25922	CAMHB[a]	0.12	11[b]	1
(0.12-0.5)		0.25	93	19
		0.5	16	10
S. aureus ATCC 29213	CAMHB	0.06	1	2
(0.12-0.5)		0.12	30	3
		0.25	58	17
		0.5	31	8
H. influenzae ATCC 49766	HTM	0.06	NA[c]	1
(0.12-0.5)		0.12		156
		0.25		551
		0.5		12
N. gonorrhoeae ATCC 49226	GC Agar	0.008	10	0
(0.008-0.03)		0.015	56	20
		0.03	34	5
S. pneumoniae ATCC 49619	CAMHB + LHB	0.06	60	20
(0.03-0.25)		0.12	60	30
		0.25	5	0
E. faecalis ATCC 29212[b]	CAMHB	1	45	10
		2	44	19
		4	18	1
		>4	13	0
P. aeruginosa ATCC 27853[b]	CAMHB	>4	120	30
H. influenzae ATCC 49247[b]	HTM	0.5	17	4
		1	32	132
		2	48	223
		4	3	287
		8	0	110
		16	0	10
		32	0	10
		64	0	1

[a] CAMHB = Cation-adjusted Mueller-Hinton broth; HTM = *Haemophilus* test medium; LHB = lysed horse blood.
[b] Organism not recommended for cefdinir quality control testing.
[c] Not applicable - 8 common lots were used by all participating laboratories.

b. Quality Control Ranges for Disk Diffusion Susceptibility Tests

Multilaboratory studies were performed to determine quality control guidelines for 5-μg cefdinir disks for *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *H. influenzae* ATCC 49766, *H. influenzae* ATCC 24927, *N. gonorrhoeae* ATCC 49226, and *S. pneumoniae* ATCC 49619. Based on the test results described below, the disk quality control ranges in Table 41 have been

proposed for cefdinir.

TABLE 41. Quality Control Guidelines for Disk Diffusion Susceptibility Tests

Organism	Quality Control Ranges (Zone Diameter in mm)
S. aureus ATCC 25923	25 to 32
E. coli ATCC 25922	24 to 28
H. influenzae ATCC 49766	24 to 31
N. gonorrhoeae ATCC 49226	40 to 49
S. pneumoniae ATCC 49619	26 to 31

S. aureus and *E. coli* were tested on Mueller-Hinton agar. Six lots of disks and 6 lots of culture media were obtained from several manufacturers, and the results of these studies were generated in 6 clinical microbiology laboratories. Each of the 6 participant laboratories performed 20 replicate tests with a unique lot of medium and 5 replicate tests with a lot of medium common to all laboratories. Results with the common lot from each laboratory were compared for significant variation. The statistic for determining zone diameter ranges is the overall median ± one half of the median of the individual laboratory ranges and/or an interval containing 95% of test values. The zone diameters of the different lots of disks did not vary significantly, and the quality control results with reference antimicrobials revealed that all lots of media were performing within NCCLS prescribed limits.

In tests with *E. coli*, the median of 450 data points was 26 mm, with a 95% confidence limit range of 24 to 28 mm encompassing 98.9% of the values.

In tests with *S. aureus*, 375 test values contributed to the database because of the large variation seen between laboratories, and because the quality control data generated at Park-Davis and collected from central laboratories testing cefdinir clinical trial isolates differed from the results from this study, a second multi-lab study was conducted in 1996 to confirm QC ranges for this organism.

Six lots of MH agar from 4 manufacturers were tested. Two participants were assigned one of 5 unique lots and a sixth lot was common to all ten laboratories. Two lots of cefdinir disks were used and cefuroxime was used as a control. No differences were seen between cefdinir disk lots,

and no lot-to-lot variability was seen between MH agars. A range of 25-31 mm was proposed by the investigator and includes 97% of the data.

One central lab's data agree with the results from the first multi-lab study, the cause of the discrepancy between the first and second multi-lab studies is unclear. However, the results of the recent ten-lab study reflect results from media currently available, and rather clearly define a range of 25-31 mm. The sponsor states that if, this range was increased by 1 mm, the majority of the "real world data" would be included. Therefore, the sponsor proposes an 8 mm range of 25-32 mm for quality control testing of *S. aureus* ATCC 25923 with cefdinir. This reviewer sees no problem with accepting these limits.

Ranges for *H. influenzae* ATCC 49766 were determined using 7 lots of HTM agar and 2 lots of disks. Six different laboratories generated 280 zone diameters. All but 2 values were in the selected range of 24 to 31 mm. The median was 27 mm, and 99.3% of the values were within the proposed range.

Testing was also conducted with *H. influenzae* ATCC 49247. As with several other cephalosporins, disk diffusion zones are not as reproducible with this strain, when compared to *H. influenzae* ATCC 49766. Therefore, the sponsor does not recommend *H. influenzae* ATCC 49247 for cefdinir quality control testing.
A similar study design yielded 300 unique-lot zone diameters with *N. gonorrhoeae* ATCC 49226 on GC agar. One of the 6 laboratories was out of range with all test drugs with the common lot of media. Results for this laboratory were not used for the final analysis. A range of 41 to 48 mm covered 94.0% of the values, and was suggested by the study coordinator (Dr R. Jones) as a possible range. However, the range of 40 to 49 mm was approved by the NCCLS in order to included 99.7% of the data.

S. pneumoniae ATCC 49619 was tested on MHA supplemented with 5% defibrinated sheep blood. There were 2 disk lots and 6 lots of Mueller-Hinton blood agar used to generate 350 zone diameters. All but 2 were within the range of 26 to 31 mm. Thus, the selected range of 26 to 31 mm covered 99.7% of all data; the median was 28 mm.

B. Bacteriological Efficacy

1. Summary of Clinical Trials

Sixteen clinical studies were conducted in order to determine the safety and efficacy of cefdinir in treating the following infections:

- Pharyngitis/Tonsillitis
- Acute Suppurative Otitis Media
- Acute Maxillary Sinusitis
- Uncomplicated Skin and Skin Structure Infections
- Community-Acquired Pneumonia
- Acute Exacerbations of Chronic Bronchitis
- Secondary Bacterial Infections of Acute Bronchitis

Capsule (adult) and suspension (pediatric) formulations were studied. In most protocols, dosages included 600 mg QD and 300 mg BID for the capsule formulation, or 14 mg/kg QD and 7 mg/kg BID for the suspension formulation. All studies tested a 10-day dosing schedule, except for pharyngitis studies which used 10-day and 5-day dosing for cefdinir. A summary of all pivotal and supportive clinical studies are shown in tables 42 and 43. A total of 11,163 patients were enrolled in these studies.

TABLE 42. List of Pivotal and Supportive Clinical Studies
Cefdinir Capsules (Adults)

Study Number	Indication	Location	Regimens	Number of Patients Enroled
983-4	Community-Acquired Pneumonia	US	Cefdinir 300 mg BID × 10d Cefaclor 500 mg TID × 10d	704
983-6	Sinusitis	US	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d Amox/Clav 500 mg TID × 10d	1229
983-7	Pharyngitis	NA	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d PenV 250 mg QID × 10d	919
983-8	Skin Infections	US	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d Cephalexin 500 mg QID × 10d	975
983-58	Pharyngitis	US	Cefdinir 300 mg BID × 5d PenV 250 mg QID × 10d	558
983-5	AECB	Non-US/US	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d Cefuroxime 250 mg BID × 10d	1045
983-26	Community-Acquired Pneumonia	Non-US	Cefdinir 300 mg BID × 10d Amox/Clav 500 mg TID × 10d	544
983-37	Sinusitis	Non-US	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d Amox/Clav 500 mg TID × 10d	569
983-38	Acute Bronchitis	US	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d	466
Other Supportive Studies				
983-16	Lower Respiratory Tract Infection	Non-US/US	Cefdinir 400 mg QD × 10d Cefdinir 600 mg QD × 10d Cefdinir 800 mg QD × 10d Cefdinir 200 mg BID × 10d Cefdinir 300 mg BID × 10d Cefdinir 400 mg BID × 10d	738

AECB = Acute exacerbations of chronic bronchitis; NA = North America; US = United States; TMP/SMX = trimethoprim/sulfamethoxazole; cefuroxime = cefuroxime axetil; amox/clav = amoxicillin/clavulanate; PenV = penicillin V-K.

TABLE 43. List of Pivotal and Supportive Clinical Studies
Cefdinir Suspension (Children)

Study Number	Indication	Location	Regimens	Number of Patients Enroled
983-10	Otitis Media	US	Cefdinir 14 mg/kg QD × 10d Cefdinir 7 mg/kg BID × 10d Amox/Clav 13.3 mg/kg TID × 10d	852
983-13	Skin Infections	US	Cefdinir 7 mg/kg BID × 10d Cephalexin 10 mg/kg QID	394
983-19	Community-Acquired Pneumonia	US	Cefdinir 7 mg/kg BID × 10d	57
983-51	Pharyngitis	NA	Cefdinir 14 mg/kg QD × 10d Cefdinir 7 mg/kg BID × 10d PenV 10 mg/kg QID × 10d	869
983-56	Pharyngitis	US	Cefdinir 7 mg/kg BID × 5d PenV 10 mg/kg QID × 10d	482
983-11	Otitis Media	Non-US	Cefdinir 14 mg/kg QD × 10d Cefdinir 7 mg/kg BID × 10d Amox/Clav 13.3 mg/kg TID × 10d	752

NA = North America; US = United States; amox/clav = amoxicillin/clavulanate; PenV = penicillin V-K.

2. Correlation of Interpretive Criteria With Therapeutic Outcome

If interpretive breakpoints are accurate, susceptibility test results should predict the therapeutic efficacy of an antibiotic. To validate proposed cefdinir interpretive breakpoints, bacteriologic eradication and clinical cure rates obtained during clinical studies were examined for correlation with MIC and disk diffusion results.

For the analyses in this section, the sponsor has included all clinically and microbiologically evaluable cefdinir-treated patients plus patients that had a baseline isolate which was intermediate or resistant to cefdinir or the comparative agent (ie, all "breakpoint evaluable" patients). Data from both monomicrobic and polymicrobic infections were used. All adult studies were conducted using a capsule formulation, and pediatric studies were conducted using a suspension formulation.

All susceptibility determinations were performed according to NCCLS methodologies. The majority of susceptibility testing for cefdinir clinical studies was performed by central laboratories. MICs were

determined by broth microdilution using dehydrated trays manufactured by Sensititre®, and 5-μg cefdinir disks were used for disk diffusion testing. Interpretive breakpoints used for clinical trial entry and patient evaluability for all pathogens isolated in US and International clinical studies are shown in Table 43. These breakpoints are used for all analyses (for fastidious and nonfastidious organisms) in this section.

TABLE 43. Interpretive Breakpoints

	Susceptible	Intermediate	Resistant
MIC	≤1 μg/mL	2 μg/mL	≥4 μg/mL
Disk Diffusion	≥20 mm	17-19 mm	≤16 mm

Barry and colleagues selected *S. pneumoniae* cefdinir MIC breakpoints different than those listed above (See page 66 of this review). However, these studies were completed near the conclusion of clinical trials. A complete discussion of interpretive criteria for *S. pneumoniae* can be found on page 114 of this review.

Tables 44 to 50 show overall trends in the data demonstrating that the above interpretive breakpoints serve as good predictors of therapeutic outcome for all target species. There is a direct correlation between a susceptible MIC or disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 44, when all organisms and both cefdinir formulations (capsule and suspension) are considered, susceptible MIC and disk diffusion results correspond with 89.0% and 89.1% bacterial eradication rates, respectively. Similarly, 86.2% and 85.9% clinical cure rates are seen with susceptible MIC and disk diffusion results, respectively.

Correlation between susceptible results and positive therapeutic outcome was generally uniform between cefdinir capsule and suspension studies (Tables 45-50). One exception is the lower eradication and clinical cure rates seen in pediatric studies for *Haemophilus* spp and *S. pneumoniae* as compared with those seen in adult studies. For data from susceptible MICs, the eradication and clinical cure rates for *Haemophilus* spp in pediatric (suspension) studies were 64.4% and 67.2% as compared to 84.6% and 78.2% in adult (capsule) studies. Similarly, the eradication and clinical cure rates for *S. pneumoniae* in pediatric studies were 60.3% and 61.3%, as compared to 93.4% and 85.0% in adult studies (Tables 46 and 47). Identical trends were seen with disk diffusion results (Tables 49 and 50). The majority of *Haemophilus* spp isolates (96%) and *S. pneumoniae* isolates (86%) from pediatric suspension studies were isolated from patients with otitis media. These results may reflect differences in pathophysiology between otitis media and other indications, or it could reflect the formulation differences between the suspension and the capsule, or it could be due to low concentrations of cefdinir in the middle ear fluid, in fact as it was stated in Table 35, the mean (range) concentration of cefdinir in the middle ear fluid was

0.23 µg/mL (0.0-0.94 µg/mL) for the 7 mg/kg dose and it was 0.63 µg/mL (0.0-1.42 µg/mL) for the 14 mg/kg dose which is well bellow the MIC_{90} susceptible breakpoint of ≤ 1 µg/mL. This issue needs to be further addressed by the pharmacologist and the medical officer. A lower eradication and clinical cure rates also were seen for these organisms with the comparative agent used in the otitis media study (amox/clav).

TABLE 44. Overall Summary of Results Relation[illegible]between Susceptibility to Cefdinir and Pathogen Eradicati[illegible] Clinical Cure Rates

All Organisms

Methodology	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
MIC	R (≥4 μg/mL)	95	80	84.2	90	63	70.0
	I (2 μg/mL)	58	47	81.0	57	44	77.2
	S (≤1 μg/mL)	3800	3382	89.0	3623	3122	86.2
Disk Diffusion	R (≤16 mm)	89	75	84.3	84	62	73.8
	I (17-19 mm)	97	81	83.5	92	72	78.3
	S (≥20 mm)	3912	3485	89.1	3716	3193	85.9

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 45. Relationship Between MIC and Path[illegible]radication and Clinical Cure Rates Cefdinir Capsule and Suspension-Treated Patients

Across Indications, Formulations, and Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≥4 μg/mL)	8	7	87.5	8	5	62.5
	I (2 μg/mL)	19	15	78.9	19	14	73.7
	S (≤1 μg/mL)	912	757	83.0	863	668	77.4
Streptococcus pneumoniae	R (≥4 μg/mL)	8	7	87.5	8	6	75.0
	I (2 μg/mL)	4	2	50.0	4	2	50.0
	S (≤1 μg/mL)	339	294	86.7	322	259	80.4
All Other Organisms	R (≥4 μg/mL)	79	66	83.5	74	52	70.3
	I (2 μg/mL)	35	30	85.7	34	28	82.4
	S (≤1 μg/mL)	2549	2331	91.4	2438	2195	90.0

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 46. Relationship Between MIC and Patho Eradication and Clinical Cure Rates Cefdinir Capsule-Trea Patients

Across Indications and Capsule Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≥4 μg/mL)	7	6	85.7	7	4	57.1
	I (2 μg/mL)	16	14	87.5	16	13	81.3
	S (≤1 μg/mL)	839	710	84.6	799	625	78.2
Streptococcus pneumoniae	R (≥4 μg/mL)	6	6	100.0	6	5	83.3
	I (2 μg/mL)	4	2	50.0	4	2	50.0
	S (≤1 μg/mL)	271	253	93.4	260	221	85.0
All Other Organisms	R (≥4 μg/mL)	66	54	81.8	61	40	65.6
	I (2 μg/mL)	28	23	82.1	27	21	77.8
	S (≤1 μg/mL)	1598	1451	90.8	1506	1313	87.2

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 47. Relationship Between MIC and Path Eradication and Clinical Cure Rates Cefdinir Suspension-T 1 Patients

Across Indications and Suspension Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≥4 μg/mL)	1	1	100.0	1	1	100.0
	I (2 μg/mL)	3	1	33.3	3	1	33.3
	S (≤1 μg/mL)	73	47	64.4	64	43	67.2
Streptococcus pneumoniae	R (≥4 μg/mL)	2	1	50.0	2	1	50.0
	I (2 μg/mL)	0			0		
	S (≤1 μg/mL)	68	41	60.3	62	38	61.3
All Other Organisms	R (≥4 μg/mL)	13	12	92.3	13	12	92.3
	I (2 μg/mL)	7	7	100.0	7	7	100.0
	S (≤1 μg/mL)	951	880	92.5	932	882	94.6

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 48. Relationship Between Zone Diameter Pathogen Eradication and Clinical Cure Rates Cefdinir Ca and Suspension-Treated Patients

Across Indications, Formulations, and Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≤16 mm)	16	14	87.5	16	14	87.5
	I (17-19 mm)	48	35	72.9	44	33	75.0
	S (≥20 mm)	961	809	84.2	908	705	77.6
Streptococcus pneumoniae	R (≤16 mm)	10	9	90.0	9	7	77.8
	I (17-19 mm)	3	2	66.7	3	2	66.7
	S (≥20 mm)	351	306	87.2	335	268	80.0
All Other Organisms	R (≤16 mm)	63	52	82.5	59	41	69.5
	I (17-19 mm)	46	44	95.7	45	37	82.2
	S (≥20 mm)	2600	2370	91.2	2473	2220	89.8

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 49. Relationship Between Zone Diameter, Pathogen Eradication and Clinical Cure Rates Cefdinir Capsule Treated Patients Across Indications and Capsule Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≤16 mm)	15	13	86.7	15	13	86.7
	I (17-19 mm)	37	30	81.1	34	28	82.4
	S (≥20 mm)	884	757	85.6	841	659	78.4
Streptococcus pneumoniae	R (≤16 mm)	6	6	100.0	6	5	83.3
	I (17-19 mm)	2	1	50.0	2	1	50.0
	S (≥20 mm)	286	267	93.4	275	233	84.7
All Other Organisms	R (≤16 mm)	51	40	78.4	47	29	61.7
	I (17-19 mm)	36	35	97.2	35	28	80.0
	S (≥20 mm)	1637	1480	90.4	1530	1330	86.9

S = Susceptible; I = Intermediate; R = Resistant.

TABLE 50. Relationship Between Zone Diameter, Pathogen Eradication and Clinical Cure Rates Cefdinir Suspension-Treated Patients

Across Indications and Suspension Dosing Regimens

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients	No. of Patients Cured	% Cured
Haemophilus spp	R (≤16 mm)	1	1	100.0	1	1	100.0
	I (17-19 mm)	11	5	45.5	10	5	50.0
	S (≥20 mm)	77	52	67.5	67	46	68.7
Streptococcus pneumoniae	R (≤16 mm)	4	3	75.0	3	2	66.7
	I (17-19 mm)	1	1	100.0	1	1	100.0
	S (≥20 mm)	65	39	60.0	60	35	58.3
All Other Organisms	R (≤16 mm)	12	12	100.0	12	12	100.0
	I (17-19 mm)	10	9	90.0	10	9	90.0
	S (≥20 mm)	963	890	92.4	943	890	94.4

S = Susceptible; I = Intermediate; R = Resistant.

Correlation between susceptible MIC and disk diffusion results and positive therapeutic outcome was also consistent between QD and BID dosing regimens for both suspension and capsule formulations, and between indications (with the exception of otitis media discussed previously).

Additionally, results were generally uniform among bacterial species. Therapeutic outcome, by formulation and by individual MICs and zone diameters for key pathogens (defined as pathogens isolated 10 or more times during clinical studies and intended for inclusion in cefdinir labeling) can be found in Tables 51 through 54. When compared with other organisms, susceptible determinations correspond to lower eradication and clinical cure rates for *Haemophilus* spp (in both capsule and suspension studies), and *S. pneumoniae* (in suspension studies). However, the sponsor states that when numbers are sufficient for statistical analysis, eradication and clinical cure rates for these organisms are equivalent to the comparative agent in all studies.

As seen in Table 44, there is an overall trend for lower eradication and cure rates with intermediate and resistant isolates. Specifically there were 153/3953 (3.9%) isolates that had resistant or intermediately resistant MICs to cefdinir (186/4098, 4.5% by disk diffusion). Among these isolates 127/153 (83%) were eradicated as compare to an eradication rate of 89% for the isolates with susceptible MICs. The cure rates were also lower for isolates with intermediate and resistant MICs (107/147, 73%) as compared to isolates with susceptible MICs with cure rate of 86%.

In summary, the data show that patients were effectively treated when pathogen isolates were determined to be susceptible using the proposed MIC and disk diffusion breakpoints. When results from all isolates are combined (Table 44), susceptible MICs and disk diffusion interpretations correlate with a 89% bacterial eradication rate, and a 86% clinical cure rate. MIC and disk diffusion susceptibility tests for cefdinir serve as good predictors of therapeutic efficacy.

TABLE 51. Relationship Between MIC Versus Pa n Eradication and Clinical Cure Rates Cefdinir Capsule-T Patients

Key Pathogens

(Page 1 of 5)

Across Indications, Capsule

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Escherichia coli	0.06	1	1	100.0	1	1	100.0
	0.125	19	14	73.7	19	14	73.7
	0.25	30	24	80.0	30	24	80.0
	0.5	11	9	81.8	11	9	81.8
	1	2	2	100.0	2	2	100.0
	4	1	1	100.0	1	1	100.0
	8	1	1	100.0	1	1	100.0
	Unknown	2	2	100.0	2	2	100.0
	Total	67	54	80.6	67	54	80.6
Haemophilus haemolyticus	0.06	2	2	100.0	2	2	100.0
	0.125	9	9	100.0	9	8	88.9
	0.25	3	3	100.0	3	3	100.0
	0.5	1	1	100.0	1	1	100.0
	Unknown	8	8	100.0	8	8	100.0
	Total	23	23	100.0	23	22	95.7
Haemophilus influenzae (β-lactamase unknown)	0.016	1	1	100.0	1	1	100.0
	0.03	2	2	100.0	2	2	100.0
	0.06	0			0		
	0.125	1	1	100.0	1	1	100.0
	0.25	1	1	100.0	1	1	100.0
	Unknown	1	1	100.0	1	0	0.0
	Total	6	6	100.0	6	5	83.3

TABLE 51. Relationship Between MIC Versus Pa n Eradication and Clinical Cure Rates Cefdinir Capsule-Ti Patients

Key Pathogens

(Page 2 of 5)

Across Indications, Capsule

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Haemophilus influenzae (β-lactamase-positive)	0.03	1	1	100.0	1	1	100.0
	0.06	1	1	100.0	1	1	100.0
	0.125	3	1	33.3	3	2	66.7
	0.25	18	15	83.3	17	14	82.4
	0.5	44	34	77.3	44	37	84.1
	1	16	14	87.5	16	12	75.0
	2	1	1	100.0	1	1	100.0
	Unknown	1	1	100.0	1	1	100.0
	Total	85	68	80.0	84	69	82.1
Haemophilus influenzae (β-lactamase-negative)	0.016	4	4	100.0	4	4	100.0
	0.03	4	4	100.0	4	1	25.0
	0.06	6	4	66.7	6	4	66.7
	0.125	43	34	79.1	42	32	76.2
	0.25	128	104	81.3	124	98	79.0
	0.5	143	108	75.5	141	106	75.2
	1	50	42	84.0	50	37	74.0
	2	8	6	75.0	8	6	75.0
	4	1	1	100.0	1	1	100.0
	8	2	1	50.0	2	1	50.0
	16	2	2	100.0	2	1	50.0
	Unknown	25	21	84.0	25	19	76.0
	Total	416	331	79.6	407	308	75.7
Haemophilus parahaemolyticus	0.008	7	7	100.0	7	7	100.0
	0.016	12	12	100.0	12	9	75.0
	0.03	7	6	85.7	7	6	85.7
	0.06	4	4	100.0	4	4	100.0
	0.125	6	6	100.0	6	4	66.7
	0.25	12	11	91.7	12	11	91.7
	0.5	2	2	100.0	2	1	50.0
	Unknown	0			0		
	Total	50	48	96.0	50	42	84.0

TABLE 51. Relationship Between MIC Versus Pa[illegible]n Eradication and Clinical Cure Rates Cefdinir Capsule-T[illegible] Patients

Key Pathogens
(Page 3 of 5)

Across Indications, Capsule

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Haemophilus parainfluenzae	0.016	5	5	100.0	5	3	60.0
	0.03	2	2	100.0	2	1	50.0
	0.06	7	7	100.0	7	4	57.1
	0.125	71	64	90.1	71	49	69.0
	0.25	163	150	92.0	162	134	82.7
	0.5	40	31	77.5	40	32	80.0
	1	16	13	81.3	15	15	100.0
	2	7	7	100.0	7	6	85.7
	4	1	1	100.0	1	1	100.0
	8	1	1	100.0	1	0	0.0
	Unknown	41	39	95.1	40	34	85.0
	Total	354	320	90.4	351	279	79.5
Klebsiella pneumoniae	0.03	1	1	100.0	1	0	0.0
	0.06	18	15	83.3	17	13	76.5
	0.125	43	39	90.7	43	33	76.7
	0.25	15	11	73.3	15	9	60.0
	0.5	2	2	100.0	2	2	100.0
	1	1	0	0.0	1	0	0.0
	2	1	1	100.0	1	1	100.0
	4	2	2	100.0	2	1	50.0
	8	0			0		
	16	1	0	0.0	1	1	100.0
	Unknown	1	1	100.0	1	1	100.0
	Total	85	72	84.7	84	61	72.6
Moraxella catarrhalis (β-lactamase-positive)	0.03	1	1	100.0	1	1	100.0
	0.06	14	13	92.9	14	11	78.6
	0.125	44	39	88.6	44	35	79.5
	0.25	51	46	90.2	49	43	87.8
	0.5	8	8	100.0	7	6	85.7
	1	3	1	33.3	3	2	66.7
	2	1	1	100.0	1	1	100.0
	Unknown	2	1	50.0	2	0	0.0
	Total	124	110	88.7	121	99	81.8

TABLE 51. Relationship Between MIC Versus Pa[illegible]n Eradication and Clinical Cure Rates Cefdinir Capsule-T[illegible] Patients

Key Pathogens
(Page 4 of 5)

Across Indications, Capsule

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Moraxella catarrhalis (β-lactamase-negative)	0.03	2	2	100.0	2	2	100.0
	0.06	8	7	87.5	7	5	71.4
	0.125	26	25	96.2	24	21	87.5
	0.25	11	11	100.0	11	10	90.9
	0.5	2	2	100.0	2	2	100.0
	Unknown	1	1	100.0	2	0	0.0
	Total	50	48	96.0	121	99	81.8
Moraxella catarrhalis (β-lactamase unknown)	0.25	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Staphylococcus aureus (oxacillin-resistant)	0.125	1	1	100.0	1	1	100.0
	0.25	1	1	100.0	1	1	100.0
	0.5	1	1	100.0	1	1	100.0
	1	0			0		
	2	0			0		
	4	2	2	100.0	2	1	50.0
	8	0			0	0	0.0
	16	3	1	33.3	3	0	0.0
	Total	8	6	75.0	8	4	50.0
Staphylococcus aureus (oxacillin-sensitive)	0.03	3	3	100.0	3	2	66.7
	0.06	1	1	100.0	2	1	100.0
	0.125	25	24	96.0	25	21	84.0
	0.25	93	86	92.5	93	81	87.1
	0.5	126	118	93.7	126	104	82.5
	1	25	23	92.0	24	22	91.7
	2	1	1	100.0	1	1	100.0
	Unknown	1	0	0.0	1	1	100.0
	Total	275	256	93.1	274	233	85.0
Staphylococcus aureus (oxacillin unknown)	0.06	4	4	100.0	4	4	100.0
	0.125	12	12	100.0	12	11	91.7
	0.25	34	31	91.2	34	31	91.2
	0.5	23	18	78.3	23	18	78.3
	1	9	7	77.8	9	6	66.7
	16	1	1	100.0	1	1	100.0
	Total	83	73	80.0	83	71	85.5

TABLE 51. Relationship Between MIC Versus P[illegible]n Eradication and Clinical Cure Rates Cefdinir Capsule-T[illegible]l Patients

Key Pathogens
(Page 5 of 5)

Across Indications, Capsule

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Streptococcus agalactiae	0.03	2	1	50.0	2	1	50.0
	0.06	25	25	100.0	25	17	68.0
	0.125	3	3	100.0	3	2	66.7
	0.25	0			0		
	0.5	0			0		
	1.0	1	1	100.0	1	0	0.0
	Total	31	30	96.8	31	20	64.5
Streptococcus pneumoniae	0.008	2	2	100.0	2	2	100.0
	0.016	14	14	100.0	13	12	92.3
	0.03	33	32	97.0	33	30	90.9
	0.06	100	94	94.0	94	80	85.1
	0.125	67	60	89.6	66	55	83.3
	0.25	33	31	93.9	33	27	81.8
	0.5	17	15	88.2	17	13	76.5
	1	5	5	100.0	5	5	100.0
	2	4	2	50.0	4	2	50.0
	4	2	2	100.0	2	2	100.0
	8	3	3	100.0	3	2	66.7
	16	1	1	100.0	1	1	100.0
	Unknown	14	14	100.0	14	12	85.7
	Total	295	275	93.2	284	240	84.5
Streptococcus pyogenes	0.008	403	368	91.3	403	380	94.3
	0.016	221	199	90.0	221	201	91.0
	0.03	31	27	87.1	31	26	83.9
	0.06	15	14	93.3	15	15	100.0
	0.125	14	13	92.9	14	13	92.9
	0.25	4	4	100.0	4	3	75.0
	0.5	6	4	66.7	6	5	83.3
	1	2	2	100.0	2	2	100.0
	Unknown	3	3	100.0	3	2	66.7
	Total	699	634	90.7	699	647	92.6

TABLE 52. Relationship Between MIC Versus P ,en Eradication and Clinical Cure Rates Cefdinir Suspensic Treated Patients

Key Pathogens
(Page 1 of 3)

Across Indications, Suspension

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Escherichia coli	0.25	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Haemophilus haemolyticus		0			0		
Haemophilus influenzae (β-lactamase unknown)	0.025	1	0	0.0	1	0	0.0
	0.5	1	0	0.0	1	0	0.0
	1	1	1	100.0	1	1	100.0
	Unknown	4	3	75.0	4	3	75.0
	Total	7	4	57.1	6	4	66.7
Haemophilus influenzae (β-lactamase-positive)	0.03	1	1	100.0	1	1	100.0
	0.125	2	2	100.0	2	2	100.0
	0.25	12	6	50.0	10	5	50.0
	0.5	9	7	77.8	8	7	87.5
	1	11	7	63.6	11	7	63.6
	Unknown	5	5	100.0	4	4	100.0
	Total	40	28	70.0	35	25	71.4
Haemophilus influenzae (β-lactamase-negative)	0.016	1	1	100.0	1	1	100.0
	0.06	2	1	50.0	2	1	50.0
	0.125	0			0		
	0.25	16	10	62.5	15	9	60.0
	0.5	9	5	55.6	8	5	62.5
	1	6	5	83.3	5	4	80.0
	2	3	1	33.3	3	1	33.3
	4	1	1	100.0	1	1	100.0
	Unknown	8	5	62.5	7	4	57.1
	Total	46	29	63.0	40	26	65.0
Haemophilus parainfluenzae	0.5	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0

TABLE 52. Relationship Between MIC Versus P[illegible]en Eradication and Clinical Cure Rates Cefdinir Suspensi[illegible] Treated Patients

Key Pathogens
(Page 2 of 3)

Across Indications, Suspension

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Klebsiella pneumoniae	0.06	1	1	100.0	1	1	100.0
	0.125	1	1	100.0	1	1	100.0
	0.25	0			0		
	0.5	0			0		
	1	1	1	100.0	1	1	100.0
	Total	3	3	100.0	3	3	100.0
Moraxella catarrhalis (β-lactamase-positive)	0.125	2	1	50.0	2	1	50.0
	0.25	12	8	66.7	11	7	63.6
	0.5	5	3	60.0	5	3	60.0
	1	2	1	50.0	2	1	50.0
	8	1	1	100.0	1	1	100.0
	Unknown	5	4	80.0	5	3	60.0
	Total	27	18	66.7	26	16	61.5
Moraxella catarrhalis (β-lactamase-negative)	0.25	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Moraxella catarrhalis (β-lactamase unknown)	4	1	0	0.0	1	0	0.0
	Total	1	0	0.0	1	0	0.0
Staphylococcus aureus (oxacillin-sensitive)	0.125	1	1	100.0	1	1	100.0
	0.25	85	84	98.8	84	82	97.6
	0.5	19	19	100.0	19	19	100.0
	Total	105	104	99.0	104	102	98.1
Staphylococcus aureus (oxacillin unknown)	0.03	1	1	100.0	1	1	100.0
	0.06	0			0		
	0.125	0			0		
	0.25	8	8	100.0	8	8	100.0
	0.5	6	2	33.3	6	2	33.3
	Unknown	1	1	100.0	1	0	0.0
	Total	16	12	75.0	16	11	68.8

TABLE 52. Relationship Between MIC Versus P[illegible]en Eradication and Clinical Cure Rates Cefdinir Suspensic[illegible] Treated Patients

Key Pathogens
(Page 3 of 3)

Across Indications, Suspension

Pathogen	MIC (μg/mL)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Streptococcus agalactiae	0.016	1	1	100.0	1	1	100.0
	0.03	1	1	100.0	1	1	100.0
	0.06	2	2	100.0	2	2	100.0
	0.125	1	1	100.0	1	1	100.0
	Total	5	5	100.0	5	5	100.0
Streptococcus pneumoniae	0.008	1	0	0.0	1	0	0.0
	0.016	2	1	50.0	2	1	50.0
	0.03	8	6	75.0	8	6	75.0
	0.06	27	16	59.3	24	14	58.3
	0.125	13	10	76.9	13	10	76.9
	0.25	9	4	44.4	8	3	37.5
	0.5	5	2	40.0	5	2	40.0
	1	3	2	66.7	3	2	66.7
	2	0			0		
	4	1	0	0.0	1	0	0.0
	8	1	1	100.0	1	1	100.0
	Unknown	10	7	70.0	9	5	55.6
	Total	80	49	61.3	73	44	60.3
Streptococcus pyogenes	0.008	756	701	92.7	755	721	95.5
	0.016	8	8	100.0	8	8	100.0
	0.03	9	9	100.0	9	9	100.0
	0.06	6	4	66.7	6	4	66.7
	0.125	1	0	0.0	1	0	0.0
	0.5	1	1	100.0	1	1	100.0
	Unknown	4	4	100.0	4	4	100.0
	Total	785	727	92.6	784	747	95.3

TABLE 53. Relationship Between Zone Diameter athogen Eradication and Clinical Cure Rates Cefdinir Cap Treated Patients

Key Pathogens
(Page 1 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Escherichia coli	19	1	1	100.0	1	1	100.0
	21	4	3	75.0	4	3	75.0
	22	4	2	50.0	4	2	50.0
	23	8	7	87.5	8	7	87.5
	24	6	3	50.0	6	4	66.7
	25	12	10	83.3	12	8	66.7
	26	12	11	91.7	12	12	100.0
	27	9	7	77.8	9	7	77.8
	28	4	3	75.0	4	3	75.0
	29	1	1	100.0	1	1	100.0
	30	5	5	100.0	5	5	100.0
	Unknown	1	1	100.0	1	1	100.0
	Total	67	54	80.6	67	54	80.6
Haemophilus haemolyticus	15	1	1	100.0	1	1	100.0
	18	2	2	100.0	2	2	100.0
	19	1	1	100.0	1	1	100.0
	20	1	1	100.0	1	1	100.0
	21	1	1	100.0	1	1	100.0
	22	1	1	100.0	1	1	100.0
	24	3	3	100.0	3	3	100.0
	25	1	1	100.0	1	1	100.0
	26	2	2	100.0	2	2	100.0
	27	2	2	100.0	2	2	100.0
	28	3	3	100.0	3	3	100.0
	29	1	1	100.0	1	1	100.0
	30	1	1	100.0	1	1	100.0
	33	1	1	100.0	1	0	0.0
	34	2	2	100.0	2	2	100.0
	Total	23	23	100.0	23	22	95.7

TABLE 53. Relationship Between Zone Diameter 'athogen Eradication and Clinical Cure Rates Cefdinir Ca[Treated Patients

Key Pathogens
(Page 2 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Haemophilus influenzae (β-lactamase unknown)	24	1	1	100.0	1	1	100.0
	26	1	1	100.0	1	1	100.0
	30	2	2	100.0	2	1	50.0
	31	1	1	100.0	1	1	100.0
	38	1	1	100.0	1	1	100.0
	Total	6	6	100.0	6	5	83.3
Haemophilus influenzae (β-lactamase-positive)	16	1	1	100.0	1	1	100.0
	18	2	2	100.0	2	2	100.0
	20	8	8	100.0	7	6	85.7
	21	6	5	83.3	6	4	66.7
	22	8	7	87.5	8	8	100.0
	23	6	5	83.3	6	5	83.3
	24	4	4	100.0	4	4	100.0
	25	18	13	72.2	18	13	72.2
	26	10	8	80.0	10	8	80.0
	27	7	5	71.4	7	6	85.7
	28	4	3	75.0	4	3	75.0
	29	2	1	50.0	2	2	100.0
	30	7	6	85.7	7	7	100.0
	32	1	0	0.0	1	0	0.0
	Unknown	1	0	0.0	1	0	0.0
	Total	85	68	80.0	84	69	82.1

TABLE 53. Relationship Between Zone Diameter Pathogen Eradication and Clinical Cure Rates Cefdinir Cap Treated Patients

Key Pathogens
(Page 3 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Haemophilus influenzae (β-lactamase-negative)	0	2	1	50.0	2	1	50.0
	14	4	3	75.0	4	3	75.0
	16	3	3	100.0	3	3	100.0
	17	3	2	66.7	3	2	66.7
	18	12	10	83.3	12	10	83.3
	19	6	3	50.0	6	5	83.3
	20	26	23	88.5	25	20	80.0
	21	26	18	69.2	26	17	65.4
	22	39	31	79.5	39	24	61.5
	23	53	45	84.9	51	44	86.3
	24	37	28	75.7	37	28	75.7
	25	38	34	89.5	38	30	78.9
	26	41	35	85.4	41	31	75.6
	27	24	19	79.2	24	21	87.5
	28	34	27	79.4	34	24	70.6
	29	12	9	75.0	12	10	83.3
	30	28	21	75.0	28	21	75.0
	31-52	25	17	68.0	25	19	76.0
	Unknown	3	2	66.7	3	1	33.3
	Total	416	331	79.6	407	308	75.7
Haemophilus parahaemolyticus	21	1	1	100.0	1	1	100.0
	22	2	2	100.0	2	2	100.0
	24	3	3	100.0	3	2	66.7
	25	1	1	100.0	1	1	100.0
	26	1	1	100.0	1	0	0.0
	27	2	2	100.0	2	2	100.0
	28	3	3	100.0	3	3	100.0
	29	2	2	100.0	2	1	50.0
	30	6	6	100.0	6	6	100.0
	31-42	29	27	93.1	29	24	82.8
	Total	50	48	96.0	50	42	84.0

TABLE 53. Relationship Between Zone Diameter Pathogen Eradication and Clinical Cure Rates Cefdinir Ca Treated Patients

Key Pathogens
(Page 4 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Haemophilus parainfluenzae	11	1	1	100.0	1	1	100.0
	13	1	1	100.0	1	1	100.0
	17	3	3	100.0	3	1	33.3
	18	5	5	100.0	5	5	100.0
	19	3	2	66.7	3	3	100.0
	20	15	14	93.3	14	11	78.6
	21	10	10	100.0	10	6	60.0
	22	20	19	95.0	20	16	80.0
	23	10	10	100.0	10	9	90.0
	24	27	23	85.2	27	20	74.1
	25	41	37	90.2	41	35	85.4
	26	35	31	88.6	35	29	82.9
	27	32	28	87.5	32	24	75.0
	28	35	30	85.7	35	26	74.3
	29	23	19	82.6	23	17	73.9
	30	44	42	95.5	44	34	77.3
	31-40	49	45	91.8	49	43	87.8
	Total	354	320	90.4	351	279	79.5
Klebsiella pneumoniae	13	1	1	100.0	1	1	100.0
	18	1	1	100.0	1	0	0.0
	20	1	1	100.0	1	1	100.0
	22	3	3	100.0	3	2	66.7
	23	5	4	80.0	5	5	100.0
	24	5	5	100.0	5	4	80.0
	25	11	8	72.7	11	8	72.7
	26	15	12	80.0	15	8	53.3
	27	12	9	75.0	12	9	75.0
	28	14	13	92.9	14	10	71.4
	29	5	4	80.0	5	5	100.0
	30	8	7	87.5	8	5	62.5
	31-36	4	4	100.0	4	4	100.0
	Total	85	72	84.7	84	61	72.6

TABLE 53. Relationship Between Zone Diameter athogen Eradication and Clinical Cure Rates Cefdinir Cap Treated Patients

Key Pathogens
(Page 5 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Moraxella catarrhalis (β-lactamase-positive)	17	1	1	100.0	1	1	100.0
	18	2	2	100.0	2	2	100.0
	20	2	0	0.0	2	2	100.0
	21	4	3	75.0	4	3	75.0
	22	11	10	90.9	11	8	72.7
	23	6	6	100.0	6	6	100.0
	24	16	16	100.0	16	15	93.8
	25	26	23	88.5	26	20	76.9
	26	20	16	80.0	20	14	70.0
	27	14	14	100.0	14	11	78.6
	28	8	6	75.0	8	7	87.5
	29	4	4	100.0	4	3	75.0
	30	3	3	100.0	3	3	100.0
	31-37	7	6	85.7	7	6	85.7
	Total	124	110	88.7	121	99	81.8
Moraxella catarrhalis (β-lactamase-negative)	20	1	1	100.0	1	1	100.0
	23	3	3	100.0	3	3	100.0
	24	3	3	100.0	3	2	66.7
	26	4	4	100.0	4	4	100.0
	27	1	0	0.0	1	0	0.0
	28	9	9	100.0	7	6	85.7
	29	2	2	100.0	2	2	100.0
	30	9	9	100.0	9	9	100.0
	31-40	18	17	94.4	18	15	83.3
	Total	50	48	96.0	47	41	87.2
Moraxella catarrhalis (β-lactamase unknown)	21	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0

TABLE 53. Relationship Between Zone Diameter athogen Eradication and Clinical Cure Rates Cefdinir Cap Treated Patients

Key Pathogens

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Staphylococcus aureus (oxacillin-resistant)	7	3	1	33.3	3	0	0.0
	13	1	1	100.0	1	1	100.0
	14	1	1	100.0	1	0	0.0
	28	1	1	100.0	1	1	100.0
	29	1	1	100.0	1	1	100.0
	31	1	1	100.0	1	1	100.0
	Total	8	6	75.0	8	4	50.0
Staphylococcus aureus (oxacillin-sensitive)	20	3	3	100.0	3	3	100.0
	22	6	6	100.0	5	5	100.0
	23	1	1	100.0	1	1	100.0
	24	5	5	100.0	5	4	80.0
	25	17	17	100.0	17	13	76.5
	26	28	26	92.9	28	27	96.4
	27	37	35	94.6	37	32	86.5
	28	42	41	97.6	42	38	90.5
	29	40	32	80.0	40	32	80.0
	30	53	50	94.3	53	43	81.1
	31-38	43	40	93.0	43	35	81.4
	Total	275	256	93.1	274	233	85.5
Staphylococcus aureus (oxacillin unknown)	12	1	1	100.0	1	1	100.0
	22	1	1	100.0	1	1	100.0
	23	1	1	100.0	1	1	100.0
	24	1	1	100.0	1	0	0.0
	25	10	8	80.0	10	8	80.0
	26	6	5	83.3	6	5	83.3
	27	14	14	100.0	14	14	100.0
	28	10	8	80.0	10	8	80.0
	29	8	7	87.5	8	6	75.0
	30	16	13	81.3	16	12	75.0
	31-38	15	14	93.3	15	15	100.0
	Total	83	73	88.0	83	71	85.5

TABLE 53. Relationship Between Zone Diameter [illegible]athogen Eradication and Clinical Cure Rates Cefdinir Cap Treated Patients

Key Pathogens
(Page 7 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Streptococcus agalactiae	20	1	1	100.0	1	0	0.0
	21	2	2	100.0	2	2	100.0
	22	1	0	0.0	1	0	0.0
	23	1	1	100.0	1	0	0.0
	24	2	2	100.0	2	1	50.0
	25	7	7	100.0	7	5	71.4
	26	3	3	100.0	3	2	66.7
	27	6	6	100.0	6	5	83.3
	28	3	3	100.0	3	2	66.7
	29	2	2	100.0	2	2	100.0
	30	3	3	100.0	3	1	33.3
	Total	31	30	96.8	31	20	64.5
Streptococcus pneumoniae	6	1	1	100.0	1	1	100.0
	7	1	1	100.0	1	1	100.0
	12	1	1	100.0	1	1	100.0
	13	1	1	100.0	1	0	0.0
	15	2	2	100.0	2	2	100.0
	17	1	1	100.0	1	1	100.0
	18	1	0	0.0	1	0	0.0
	20	3	2	66.7	3	2	66.7
	21	4	4	100.0	4	4	100.0
	22	3	3	100.0	3	3	100.0
	23	4	4	100.0	4	4	100.0
	24	14	13	92.9	14	13	92.9
	25	13	12	92.3	13	9	69.2
	26	20	20	100.0	20	18	90.0
	27	11	10	90.9	11	9	81.8
	28	16	14	87.5	16	10	62.5
	29	17	17	100.0	17	14	82.4
	30	30	29	96.7	30	27	90.0
	31-51	151	139	92.1	149	129	86.6
	Unknown	1	1	100.0	1	1	100.0
	Total	295	275	93.2	284	240	84.5

TABLE 53. Relationship Between Zone Diameter, Pathogen Eradication and Clinical Cure Rates Cefdinir Ca; Treated Patients

Key Pathogens
(Page 8 of 8)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogen	No. of Patients Cured	% Cured
Streptococcus pyogenes	15	1	1	100.0	1	1	100.0
	21	2	1	50.0	2	2	100.0
	22	2	2	100.0	2	2	100.0
	23	4	3	75.0	4	3	75.0
	24	6	6	100.0	6	4	66.7
	25	10	9	90.0	10	9	90.0
	26	15	12	80.0	15	12	80.0
	27	28	27	96.4	28	25	89.3
	28	51	46	90.2	51	48	94.1
	29	41	39	95.1	41	38	92.7
	30	110	102	92.7	110	99	90.0
	31-50	429	386	90.0	429	404	94.2
	Total	699	634	90.7	699	647	92.6

TABLE 54. Relationship Between Zone Diameter and ogen Eradication and Clinical Cure Rates Cefdinir Suspension-Treated Patients

Key Pathogens
(Page 1 of 4)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogens	No. of Patients Cured	% Cured
Escherichia coli	26	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Haemophilus influenzae (β-lactamase unknown)	16	1	1	100.0	1	1	100.0
	18	1	1	100.0	1	1	100.0
	20	2	2	100.0	2	2	100.0
	26	2	0	0.0	1	0	0.0
	Unknown	1	0	0.0	1	0	0.0
	Total	7	4	57.1	6	4	66.7
Haemophilus influenzae (β-lactamase-positive)	18	3	1	33.3	3	1	33.3
	19	3	0	0.0	2	0	0.0
	20	7	5	71.4	7	5	71.4
	21	1	1	100.0	1	1	100.0
	22	5	4	80	5	4	80.0
	23	2	2	100.0	2	2	100.0
	24	8	7	87.5	7	6	85.7
	25	7	6	85.7	6	5	83.3
	26	1	0	0.0	1	0	0.0
	29	1	1	100.0	1	1	100.0
	30	1	0	0.0	1	0	0.0
	Unknown	1	1	100.0	1	1	100.0
	Total	40	28	70.0	35	25	71.4
Haemophilus influenzae (β-lactamase-negative)	18	4	3	75.0	4	3	75.0
	20	7	3	42.9	6	3	50.0
	21	2	2	100.0	2	2	100.0
	22	6	4	66.7	6	4	66.7
	23	4	4	100.0	4	4	100.0
	24	7	5	71.4	7	5	71.4

TABLE 54. Relationship Between Zone Diameter and Pathogen Eradication and Clinical Cure Rates Cefdinir Suspension-Treated Patients

Key Pathogens
(Page 2 of 4)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogens	No. of Patients Cured	% Cured
Haemophilus influenzae (β-lactamase-negative) (continued)	25	4	3	75.0	4	3	75.0
	26	4	1	25.0	3	1	33.3
	27	2	1	50.0	2	1	50.0
	31	1	0	0.0	1	0	0.0
	33	1	0	0.0	1	0	0.0
	45	1	0	0.0	1	0	0.0
	Unknown	3	3	100.0	2	2	100.0
	Total	46	29	63.0	40	26	65.0
Haemophilus parainfluenzae	26	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Klebsiella pneumoniae	22	1	1	100.0	1	1	100.0
	28	1	1	100.0	1	1	100.0
	30	1	1	100.0	1	1	100.0
	Total	3	3	100.0	3	3	100.0
Moraxella catarrhalis (β-lactamase unknown)	21	1	0	0.0	1	0	0.0
	Total	1	0	0.0	1	0	0.0
Moraxella catarrhalis (β-lactamase-positive)	15	1	1	100.0	1	1	100.0
	18	2	1	50.0	2	1	50.0
	20	1	0	0.0	1	0	0.0
	21	3	2	66.7	3	2	66.7
	22	2	2	100.0	2	2	100.0
	23	2	2	100.0	2	2	100.0
	24	3	2	66.7	3	1	33.3
	25	4	4	100.0	4	4	100.0
	26	2	1	50.0	2	1	50.0
	27	2	1	50.0	2	0	0.0
	28	3	2	66.7	3	2	66.7
	29	1	0	0.0	1	0	0.0
	30	1	0	0.0	1	0	0.0
	Total	27	18	66.7	26	16	61.5

TABLE 54. Relationship Between Zone Diameter and Pathogen Eradication and Clinical Cure Rates Cefdinir Suspension-Treated Patients

Key Pathogens
(Page 3 of 4)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogens	No. of Patients Cured	% Cured
Moraxella catarrhalis (β-lactamase-negative)	40	1	1	100.0	1	1	100.0
	Total	1	1	100.0	1	1	100.0
Staphylococcus aureus (oxacillin unknown)	24	1	0	0.0	1	0	0.0
	26	1	1	100.0	1	1	100.0
	28	2	1	50.0	2	1	50.0
	29	2	2	100.0	2	2	100.0
	30	2	1	50.0	2	1	50.0
	31-39	8	7	87.5	8	6	75.0
	Total	16	12	75.0	16	11	68.8
Staphylococcus aureus (oxacillin-sensitive)	26	2	2	100.0	2	2	100.0
	27	9	9	100.0	8	8	100.0
	28	5	5	100.0	5	4	80.0
	29	12	12	100.0	12	12	100.0
	30	28	28	100.0	28	28	100.0
	31-38	49	48	98.0	49	48	98.0
	Total	105	104	99.0	104	102	98.1
Streptococcus agalactiae	26	1	1	100.0	1	1	100.0
	27	1	1	100.0	1	1	100.0
	31	2	2	100.0	2	2	100.0
	34	1	1	100.0	1	1	100.0
	Total	5	5	100.0	5	5	100.0
Streptococcus pneumoniae	12	3	3	100.0	2	2	100.0
	16	1	0	0.0	1	0	0.0
	17	1	1	100.0	1	1	100.0
	20	1	1	100.0	1	1	100.0
	22	3	2	66.7	3	2	66.7
	23	2	0	0.0	2	0	0.0
	25	5	2	40.0	5	2	40.0
	26	4	3	75.0	4	3	75.0

TABLE 54. Relationship Between Zone Diameter and Pathogen Eradication and Clinical Cure Rates Cefdinir Suspension-Treated Patients

Key Pathogens
(Page 4 of 4)

Pathogen	Zone Diameter (mm)	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated	% Eradicated	No. of Patients With Pathogens	No. of Patients Cured	% Cured
Streptococcus pneumoniae (continued)	27	2	1	50.0	2	1	50.0
	28	7	3	42.9	7	3	42.9
	29	1	0	0.0	1	0	0.0
	30	6	5	83.3	6	3	50.0
	31-46	34	22	64.7	32	22	68.8
	Unknown	10	6	60.0	9	6	66.7
	Total	80	49	61.3	73	44	60.3
Streptococcus pyogenes	20	1	1	100.0	1	1	100.0
	22	1	1	100.0	1	1	100.0
	24	1	0	0.0	1	0	0.0
	25	3	3	100.0	3	3	100.0
	26	5	4	80.0	5	5	100.0
	27	6	6	100.0	6	6	100.0
	28	16	16	100.0	16	16	100.0
	29	23	22	95.7	23	23	100.0
	30	129	119	92.2	129	124	96.1
	31-39	600	555	92.5	600	569	94.8

3. Discussion of MIC Interpretive Breakpoints for *Streptococcus pneumoniae*

Due to the emergence of penicillin-resistant strains of *Streptococcus pneumoniae*, the NCCLS began recommending in 1993 that separate interpretive breakpoints be determined for *S. pneumoniae* for all relevant antibiotics by testing large numbers of strains with varying resistance to penicillin. Because these recommendations did not exist when clinical trials with cefdinir began in 1990, the breakpoints used for all other organisms (≤1 µg/mL = Susceptible, 2 µg/mL = Intermediate, and ≥4 µg/mL = Resistant) were used as well for *S. pneumoniae*.

In 1994, Barry, et al, tested cefdinir against 350 strains of *S. pneumoniae* with varying penicillin resistance levels (see discussion on page 69 of this review). Interpretive breakpoints 1 dilution lower than those recommended for all other organisms were suggested for the interpretation of *S. pneumoniae* cefdinir MIC data (≤0.5 µg/mL = Susceptible, 1 µg/mL = Intermediate, and ≥2 µg/mL = Resistant). According to the sponsor, when these breakpoints were applied, all 199 penicillin-susceptible strains tested susceptible to cefdinir and all 64 penicillin-resistant strains tested resistant to cefdinir. Of the 87 strains with intermediate susceptibility to penicillin, 68 (78%) tested susceptible, 5 (6%) tested intermediate, and 14 (16%) tested resistant to cefdinir.

As seen in Table 55, because of the small number of relevant isolates in the resistant and intermediate categories, this analysis is not significantly affected when the lower breakpoints suggested by Barry are used.

TABLE 55. Correlation Between Therapeutic Outcome and Different Interpretive Criteria for *Streptococcus pneumoniae* Cefdinir Capsule- and Suspension-Treated Patients

Organism	Cefdinir Susceptibility	Pathogen Eradication Rate		Clinical Cure Rate	
		No. of Pathogens Eradicated	% Eradicated	No. of Patients Cured	% Cured
Streptococcus pneumoniae	R (≥4 µg/mL)	7/8	87.5	6/8	75.0
	I (2 µg/mL)	2/4	50.0	2/4	50.0
	S (≤1 µg/mL)	294/339	86.7	259/322	80.4
S. pneumoniae	R (≥2 µg/mL)	9/12	75.0	8/12	66.7
	I (1 µg/mL)	7/9	87.5	7/8	87.5
	S (≤0.5 µg/mL)	287/331	86.7	255/319	79.9

S = Susceptible; I = Intermediate; R = Resistant.

Clinical trial data were also analyzed based on penicillin susceptibility of *S. pneumoniae* isolates. Penicillin MICs for *S. pneumoniae* were not routinely determined during clinical trials, but all available isolates (297) were tested after the conclusion of the studies. Of these 297, only 24 isolates from cefdinir-treated patients were found to be penicillin-intermediate or -resistant. Penicillin MICs for all cefdinir-treated patients with penicillin-intermediate and -resistant isolates and corresponding cefdinir

MICs and therapeutic outcomes are shown in Table 56.

TABLE 56. Therapeutic Outcome of Cefdinir-Treated Patients With Documented Penicillin-Intermediate and -Resistant Strains of *Streptococcus pneumoniae* All Cefdinir-Treated Patients

Patient No. 983-[a]	Penicillin MIC	Penicillin Interpretation[b]	Cefdinir MIC	Clinical Outcome	Microbiologic Outcome
4-63-55	0.12	I	0.25	Cure	Eradication
4-11-25	0.25	I	0.12	Cure	Eradication
4-73-8	0.25	I	0.25	Cure	Eradication
4-5-58	0.5	I	0.25	Cure	Eradication
4-16-16	0.5	I	0.5	Cure	Eradication
4-27-28	0.5	I	0.5	Failure	Eradication
4-5-42	1	I	2	Cure	Eradication
4-14-19	2	R	8	Failure	Eradication
6-36-229	0.5	I	0.5	Cure	Eradication
6-41-213	0.5	I	0.5	Failure	Eradication
6-36-234	2	R	2	Failure	Persistence
6-42-210	0.5	I	0.25	Failure	Persistence
6-36-235	4	R	16	Cure	Eradication
6-36-237	4	R	2	Cure	Eradication
6-50-210	4	R	4	Cure	Eradication
5-6-49	0.12	I	0.25	Cure	Eradication
5-17-121	0.12	I	0.5	Cure	Eradication
5-24-13	4	R	1	Cure	Eradication
5-24-15	1	I	0.5	Cure	Eradication
26-21-11	4	R	8	Cure	Eradication
37-8-31	0.12	I	4	Cure	Eradication
37-8-52	1	I	4	Cure	Eradication
37-14-15	0.12	I	0.5	Cure	Eradication
37-17-15	0.12	I	0.12	Cure	Eradication

[a] Study number-site number-patient number
[b] S = Sensitive (MIC ≤0.06 μg/mL); I = Intermediate (MIC = 0.1-1 μg/mL); R = Resistant (MIC ≥2 μg/mL).

In addition to the patients described above, 1 cefdinir-treated patient with otitis media (983-10-4-21) had an oxacillin-resistant *S. pneumoniae* isolated at baseline (zone diameter 13 mm). A penicillin MIC was not determined. Follow-up tympanocentesis proved that this organism was eradicated.

A summary of the therapeutic outcome for all cefdinir-treated patients with penicillin-intermediate and -resistant strains of *S. pneumoniae* is shown in Table 57. Response to cefdinir treatment for patients with penicillin-intermediate isolates was good with 15 of 17 strains eradicated and 15 of 17 patients cured clinically. Six of 7 penicillin-resistant strains were eradicated and 5 of the 7 patients were clinically cured.

TABLE 57. Pathogen Eradication and Clinical Cure Rates of Penicillin-Intermediate and -Resistant Strains of *Streptococcus pneumoniae* All Cefdinir-Treated Patients

Treatment Group	Penicillin Susceptibility	Pathogen Eradication Rate		Clinical Cure Rate	
		No. of Pathogens Eradicated	% Eradicated	No. of Patients Cured	% Cured
Cefdinir 600 mg QD	R (≥2 μg/mL)	0/1	0	0/1	0
	I (0.1-1 μg/mL)	5/5	100	4/5	80
	S (≤0.06 μg/mL)	44/49	90	38/47	81
Cefdinir 300 mg BID	R (≥2 μg/mL)	6/6	100	5/6	83
	I (0.1-1 μg/mL)	10/12	83	11/12	92
	S (≤0.06 μg/mL)	101/112	90	96/111	86
Total Cefdinir	R (≥2 μg/mL)	6/7	86	5/7	71
	I (0.1-1 μg/mL)	15/17	88	15/17	88
	S (≤0.06 μg/mL)	145/161	90	134/158	85

S = Susceptible; I = Intermediate; R = Resistant

According to the sponsor, although the clinical data show that cefdinir effectively eradicates penicillin-intermediate and -resistant strains of *S. pneumoniae* in many cases, the numbers are too small to make any definitive conclusions regarding treatment of penicillin-intermediate and -resistant strains with cefdinir, or to confirm either the *S. pneumoniae* interpretive breakpoints used during cefdinir clinical trials or those suggested by Barry. Like all cephalosporins, cefdinir shows cross-resistance with penicillin. To avoid possible therapy failures due to penicillin-resistant strains, the most conservative approach would be to suggest that only strains that are penicillin-susceptible be treated with cefdinir until additional data are available.

C. *In Vitro* Studies Conducted During Clinical Trials

1. *In Vitro* Susceptibility Summary

Based on achievable plasma concentrations, the following MIC interpretive breakpoints have been proposed for cefdinir: Susceptible, MIC ≤1 μg/mL; Intermediate, MIC = 2 μg/mL; and Resistant, MIC ≥4 μg/mL. Using the above interpretive criteria, cefdinir showed good in vitro activity against most of the pathogens encountered during clinical studies. According to the sponsor, of the 8061 clinical trial isolates for which a cefdinir MIC was determined at baseline, 95% were susceptible to cefdinir, with MIC

values ≤1 μg/mL. Data for the most commonly encountered pathogens are summarized in Table 58.

Cefdinir was active against most gram-positive bacteria including *S. aureus* (MIC_{90} = 0.5 μg/mL), *Streptococcus agalactiae* (MIC_{90} = 0.125 μg/mL), *S. pneumoniae* (MIC_{90} = 0.5 μg/mL), and *S. pyogenes* (MIC_{90} = 0.016 μg/mL). In addition, fastidious gram-negative bacteria were susceptible with MIC_{90}s for *H. influenzae* of 1.0 μg/mL, and *H. parainfluenzae* and *M. catarrhalis* of 0.5 μg/mL. Included within these fastidious organisms were many β-lactamase-producing organisms. Cefdinir showed poor activity against *E. faecalis* and *Pseudomonas aeruginosa* clinical study isolates, corresponding with results obtained in earlier preclinical *in vitro* studies.

Cefdinir was also active against some of the *Enterobacteriaceae*. Ninety percent of *E. coli* and *Proteus mirabilis* isolates were susceptible to cefdinir at concentrations of 0.5 μg/mL, and 90% of *K. pneumoniae* and *Klebsiella oxytoca* isolates were susceptible at 0.25 μg/mL. Cefdinir showed poor activity against *Enterobacter* spp. MIC_{90}s for these isolates ranged from 2.0 μg/mL for *E. agglomerans* to 16.0 μg/mL for *E. cloacae*. Cefdinir was also inactive against the *Serratia* spp. (MIC_{90} = 16.0 μg/mL).

TABLE 58. Cefdinir Activity Against Clinical Study Isolates

Pathogen[a]	No. of Times Isolated	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC Range (μg/mL)
Gram-Positive				
Enterococcus faecalis	65	4.0	8.0	0.5-16.0
Staphylococcus aureus	1108	0.016	0.5	0.016-0.5
Staphylococcus epidermidis	14	0.125	16.0	0.03-16.0
Streptococcus agalactiae	109	0.06	0.125	0.016-2.0
Streptococcus anginosus	6	ND[b]	ND	0.16-16.0
Streptococcus Group G	14	0.03	0.03	0.016-1.0
Streptococcus pneumoniae	701	0.06	0.5	0.008-16.0
Streptococcus pyogenes	2750	0.008	0.016	0.008-2.0
Gram-Negative (Non-Enterobacteriaceae)				
Acinetobacter anitratus	35	4.0	8.0	0.06-16.0
Acinetobacter lwoffii	24	1.0	4.0	0.125-16.0
Haemophilus haemolyticus	23	0.125	0.25	0.03-0.5
Haemophilus influenzae	1139	0.5	1.0	0.008-16.0
Haemophilus parahaemolyticus	108	0.06	0.5	0.008-1.0
Haemophilus parainfluenzae	661	0.25	0.5	0.008-8.0
Moraxella catarrhalis	375	0.25	0.5	0.008-16.0
Neisseria lactamica	5	ND	ND	0.03-0.125
Neisseria meningitidis	12	0.008	0.016	0.008-0.25
Neisseria mucosa	10	0.125	0.5	0.016-0.5
Pasteurella multocida	5	ND	ND	0.016-1.0
Pseudomonas aeruginosa	23	16.0	16.0	16.0-16.0
Xanthomonas maltophilia	5	ND	ND	0.125-16.0
Enterobacteriaceae				
Citrobacter diversus	21	0.125	0.25	0.125-0.5
Citrobacter freundii	27	0.5	16.0	0.125-16.0
Enterobacter aerogenes	43	1.0	4.0	0.25-16.0
Enterobacter agglomerans	43	0.25	2.0	0.008-16.0
Enterobacter cloacae	86	2.0	16.0	0.06-16.0
Escherichia coli	169	0.25	0.5	0.03-16.0
Escherichia hermanii	9	ND	ND	0.06-1.0
Klebsiella oxytoca	54	0.125	0.25	0.03-0.25
Klebsiella pneumoniae	173	0.125	0.25	0.016-16.0
Morganella morganii	6	ND	ND	0.06-16.0
Proteus mirabilis	68	0.125	0.5	0.03-16.0
Proteus vulgaris	8	ND	ND	0.125-8.0
Serratia marcescens	29	4.0	16.0	0.008-16.0
Serratia proteamaculans	11	2.0	16.0	0.5-16.0
All Organisms	8061	0.125	0.5	0.008-16.0

[a] All pathogens isolated 5 or more times during clinical studies are listed.

[b] MIC_{50} and MIC_{90} not determined for <10 isolates

2. Comparison of *In Vitro* Preclinical and Clinical Trial Data for Pathogens Included in Cefdinir Labeling

A comparison of cefdinir MIC results, for all organisms (that were included in cefdinir labeling by the sponsor), from preclinical *in vitro* studies and from clinical trials are shown in Table 59. According to the sponsor, only organisms that were considered pathogens for the disease state from which they were isolated were included in the clinical trial data analysis.

Cefdinir MIC results were roughly similar from preclinical studies and clinical trials for the isolates for which complete data was available. However, the MIC_{90} for *Staphylococcus epidermidis* was higher from clinical trials when compared with that determined in preclinical studies (16 vs 4 μg/mL for isolates where methicillin susceptibility is unknown). According to the sponsor, because only organisms that were considered pathogens for the disease state from which they were isolated were used in the analysis, the number of *S. epidermidis* isolates in the clinical trial data was very low (N = 14). When all *S. epidermidis* isolates (N = 229) were included in the calculation, regardless of whether or not they were considered pathogens, the MIC_{90} was 2.0 μg/mL, and the MIC_{50} was 0.06 μg/mL. Also, the clinical trial data included all isolates regardless of oxacillin susceptibility, which results in a higher MIC_{90} for this organism.

From the microbiological perspective, the *in vitro* data shown in Table 59, and the pathogen eradication and clinical cure rates seen in clinical trials, the following organisms are candidates for inclusion in the "INDICATIONS AND USAGE" section of the cefdinir labeling: *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus agalactiae*, *S. pneumoniae* (penicillin-susceptible strains), *S. pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *H. influenzae* (including β-lactamase producing strains), *H. parainfluenzae* (including β-lactamase producing strains), and *Moraxella catarrhalis* (including β-lactamase producing strains).

The safety and effectiveness of cefdinir has been evaluated in clinical trials and is currently under review. The results suggest that cefdinir exhibits *in vitro* MICs of 1 μg/mL or less against ≥90% of the strains of the following organisms: methicillin-susceptible strains of *Staphylococcus epidermidis*, viridans group streptococci, *Citrobacter diversus*, and *Proteus mirabilis*. These organisms should be included in the *in vitro* section of the cefdinir labeling.

TABLE 59. Comparison of Cefdinir MICs for Labeled Pathogens from Pre-clinical Studies and Clinical Trials

(Page 1 of 2)

Organism	Preclinical Studies			Clinical Trial Results			
	N	Range	MIC_{90}	N	Range	MIC_{50}	MIC_{90}
Pathogens on Indications and Usage List in Labeling							
Staphylococcus aureus							
Methicillin/oxacillin unspecified	1865	≤0.002->128	0.8	1108	0.016-0.5	0.016	0.5
Methicillin/oxacillin-resistant	925	0.2->128	>64				
Methicillin/oxacillin-susceptible	1609	0.008-25	0.5				
Streptococcus agalactiae	402	≤0.008-0.5	≤0.03	109	0.16-2.0	0.06	0.12
Streptococcus pneumoniae							
Penicillin susceptibility unspecified	744	≤0.002-8.0	0.1	701	0.008-16.0	0.06	0.5
Penicillin-susceptible	858	0.008-1	0.12				
Penicillin-intermediate	319	0.015-16	4.0				
Penicillin-resistant	404	≤0.03->16	8.0				
Streptococcus pyogenes	1204	≤0.002-6	≤0.03	2750	0.008-2.0	0.008	0.016
Escherichia coli	3248	0.008-128	0.5	169	0.03-16.0	0.25	0.5
Haemophilus influenzae	2035	≤0.015-25	0.5	1139	0.008-16.0	0.5	1.0
Haemophilus parainfluenzae	62	0.03-1	0.05	661	0.008-8.0	0.25	0.5
Klebsiella pneumoniae	1591	≤0.01->128	0.40	173	0.016-16.0	0.12	0.25
Moraxella catarrhalis	1088	≤0.01-32	0.25	375	0.008-16.0	0.25	0.5
Pathogens on In Vitro List in Labeling							
Gram-Positive Aerobes							
Gemella morbillorum	10	0.05-0.4	0.4	4	0.06-4.0	ND[a]	ND
Staphylococcus epidermidis							
Methicillin/oxacillin unspecified	526	≤0.025->128	4.0	14	0.03-16.0	0.12	16.0
Methicillin/oxacillin-resistant	89	0.03->128	>100	0			
Methicillin/oxacillin-susceptible	118	0.01-3.1	0.1	0			
Staphylococcus haemolyticus							
Methicillin/oxacillin unspecified	208	≤0.025->128	>64	0			
Methicillin/oxacillin-resistant	7	16->128	ND[a]	0			
Methicillin/oxacillin-susceptible	33	0.03->64	0.5	0			
Staphylococcus hominis							
Methicillin/oxacillin unspecified	17	0.03-0.4	0.1	1	0.25	ND	ND
Methicillin/oxacillin-susceptible	12	0.03-0.12	0.12	0			
Streptococcus anginosus	52	0.016-0.25	0.1	6	0.16-16.0	ND	ND
Streptococcus constellatus	25	≤0.025-0.1	0.1	0			
Streptococcus Group C	10	≤0.016-0.03	ND	3	0.016-0.25	ND	ND
Streptococcus Group G	32	0.008-0.03	0.016	14	0.016-1.0	0.03	0.03
Streptococcus intermedius	25	≤0.025-0.2	0.05	0			
Streptococcus mitis	27	0.016-6.25	0.4	3	0.016-1.0	ND	ND
Streptococcus sanguis	31	≤0.025-0.2	0.05	0			

[a] MIC_{50} and MIC_{90} not determined for <10 isolates

TABLE 59. Comparison of Cefdinir MICs for Labeled Pathogens from Pre-clinical Studies and Clinical Trials

(Page 2 of 2)

Organism	Preclinical Studies			Clinical Trial Results			
	N	Range	MIC_{90}	N	Range	MIC_{50}	MIC_{90}
Gram-Negative Aerobes							
Aeromonas hydrophila	72	≤0.03->16.0	0.5	2	0.25-0.5	ND*	ND
Citrobacter diversus	141	≤0.015-64	0.25	21	0.12-0.5	0.12	0.25
Enterobacter sakazakii	13	0.06-2.0	0.25	2	0.5-0.5	ND	ND
Escherichia hermanii	0			9	0.06-1.0	ND	ND
Klebsiella oxytoca	559	≤0.008-128	0.25	54	0.03-0.25	0.125	0.25
Pantoea (Enterobacter) agglomerans	31	≤0.03->4.0	0.5	43	0.008-16.0	0.25	2.0
Pasteurella multocida	9	0.008-0.12	ND	5	0.016-1.0	ND	ND
Proteus mirabilis	1224	≤0.01-100	0.13	68	0.03-16.0	0.125	0.5
Anaerobes							
Peptostreptococcus anaerobius	28	≤0.025-12.5	0.8	1	0.06	ND	ND
Peptostreptococcus asaccharolyticus	39	≤0.025-0.4	0.2	0			
Peptostreptococcus magnus	51	≤0.025-16.0	0.4	0			
Peptostreptococcus micros	16	≤0.025-0.1	≤0.025	1	0.06	ND	ND

* MIC_{50} and MIC_{90} not determined for <10 isolates

V. CONCLUSIONS

- Cefdinir is a new cephalosporin with a good *in vitro* spectrum against gram-negative and -positive bacteria. The MIC_{90} for common respiratory tract and skin and skin structure pathogens including methicillin-susceptible staphylococci, streptococci, *Moraxella, Haemophilus, Escherichia coli,* and *Klebsiella pneumoniae* is ≤1.0 μg/mL.

- Cefdinir is especially effective against methicillin-susceptible *Staphylococcus aureus*. This enhanced activity is due to cefdinir's relative stability to the β-lactamases produced by staphylococci

- Cefdinir is rapidly absorbed, with maximal plasma concentrations occurring 2 to 4 hours postdose. Plasma cefdinir concentrations increase with dose, but changes are less than dose-proportional. Mean cefdinir C_{max} is 1.6 μg/mL following a single 300-mg capsule dose and 2.9 μg/mL following a single 600-mg capsule.

- Cefdinir penetrates into suction-induced skin blister fluid, tonsil tissue, bronchial mucosa, and epithelial lining fluid, in concentrations equal or greater than the MICs of the usual pathogens at these sites. However, cefdinir penetrates into sinus tissue, and middle ear effusion in concentrations

generally less than the MICs of the usual pathogens at these sites. Cefdinir is not detected in the milk of nursing women.

- Cefdinir shows excellent β-lactamase stability to common gram-negative β-lactamases of the penicillinase type. Against cephalosporinase-type β-lactamases, a varied response (moderate to good) is observed and against oxyiminocephalosporinases, poor to fair stability is seen.

- Cefdinir MICs are generally stable to medium and pH changes, serum and urine effects, and addition of 5% CO_2 atmosphere. Activity against *Enterococcus faecalis* is enhanced in MHA with 5% sheep blood.

- Cefdinir shows good *in vitro* activity against the majority of gram-negative and gram-positive organisms isolated during clinical trials. Ninety percent of the 8061 clinical trial isolates are susceptible to cefdinir at concentrations of ≤0.5 μg/mL, and 95% are susceptible at ≤1.0 μg/mL. *Enterococcus* spp, *Enterobacter* spp, and *Pseudomonas aeruginosa* clinical trial isolates are resistant to cefdinir with MIC_{90}s ranging from 2.0- 16 μg/mL.

- Interpretive breakpoints proposed by the sponsor for nonfastidious and *Haemophilus* spp. are as follows:

	Susceptible	Intermediate	Resistant
MIC	≤1 μg/mL	2 μg/mL	≥4 μg/mL
Disk Diffusion	≥20 mm	17-19 mm	≤16 mm

Using these proposed susceptible interpretive breakpoints for cefdinir, MIC and disk diffusion results correlate with positive therapeutic outcomes for both capsule and suspension cefdinir formulations. When results for all isolates are combined, susceptible MIC and disk diffusion interpretations correlate with an 89% bacterial eradication rate and an 86% clinical cure rate. In general, the correlation between susceptible results and positive therapeutic outcome was consistent between the capsule and suspension formulations, between QD versus BID dosing, and among bacterial species. Thus the data show that patients were effectively treated when isolates were judged susceptible based on the proposed breakpoints. The proposed breakpoints may stand as is with the exception of *Haemophilus* spp. which will have only susceptible breakpoint due to lack of >20 resistant isolates.

- Lower eradication and clinical cure rates are seen with intermediate and resistant isolates. However, the majority of these isolates responded to cefdinir therapy regardless of these classifications.

- Clinical data show that cefdinir eradicates penicillin-intermediate and -resistant strains of *S. pneumoniae* in many cases, but the numbers of isolates from clinical trials are too small to confirm interpretive breakpoints for this organism. Cefdinir shows cross-resistance with penicillin when testing *S. pneumoniae*. To avoid possible therapy failures due to penicillin-resistant strains, the most conservative approach would be to suggest that only penicillin-susceptible strains be treated with cefdinir until additional data are available.

- No testing for *Neisseria gonorrhoeae* is needed since the sponsor is not seeking an indication for treatment of this organism.

- The quality control ranges shown in Table 60 have been developed under standardized conditions for quality control of MIC and disk diffusion testing with cefdinir. These ranges may be used by the clinical laboratories as they stand.

TABLE 60. Quality Control Ranges for Cefdinir

Organism	MIC range (μg/mL)	Disk Diffusion Range (mm)
E. coli ATCC 25922	0.12-0.5	24-28
S. aureus ATCC 29213	0.12-0.5	NA
S. aureus ATCC 25923	NA	25-32
H. influenzae ATCC 49766	0.12-0.5	24-31
S. pneumoniae ATCC 49619	0.03-0.25	26-31

NA = Not applicable.

- The rate of resistance development to cefdinir during clinical trials was extremely low at 0.2%. The organism that most frequently developed resistance was *Haemophilus influenzae*, with a resistance development rate of 0.5%.

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/S/

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