Indication: Uncomplicated Skin and Skin Structure Infections.

Title and Study Number: Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefadroxil Monohydrate in the Treatment of Patients with Uncomplicated Skin or Skin Structure Infections (Protocol No. Cef-97-011).

Objective: To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and cefadroxil monohydrate 500 mg BID in the treatment of patients with uncomplicated skin or skin structure infection.

Study Design: This was a phase III, randomized, double-blind, active-controlled, parallel-group, multi-center study in outpatients with uncomplicated skin or skin structure infections. Approximately 70 investigators were to enroll 840 eligible patients. Patients who met the selection criteria were randomly assigned in a 1:1:1 ratio to receive either cefditoren pivoxil 200 mg BID for 10 days, cefditoren pivoxil 400 mg BID for 10 days, or cefadroxil monohydrate 500 mg for 10 days. Patients returned to the investigator's office for periodic microbiologic evaluation and assessment of the clinical signs and symptoms of infection.

Protocol Overview

Population and Inclusion/Exclusion Criteria: These criteria were similar to those stated in the previous study (protocol Cef-97-009.

Discontinuation Criteria:

Patients were removed from the study immediately if any of the following occurred:

- There was insufficient improvement in the patient's infection. If the patient had at least 2 consecutive days of therapy, the clinical response was rated as "Clinical Failure."
- The investigator believed discontinuation was in the best interest of the patient (e.g., due to an adverse event or clinically significant abnormal laboratory test during treatment).
- The patient (or his/her parent or legal guardian) requested withdrawal from the study.

If the study drug therapy was prematurely discontinued, the primary reason for discontinuation was recorded on the appropriate CRF. A patient who prematurely discontinued study drug was to return to the investigator's office within 48 hours after discontinuation of study drug and the procedures outlined for the Post-Therapy Visit, including clinical evaluations and infection site specimens for culture, were to be completed. A clinical response to therapy was to be assigned. These evaluations were to be made before initiation of any new therapeutic measures, but were not in any way to delay institution of any new therapeutic modalities which, in the investigator's opinion, were necessary. If the patient's clinical response at the Post-Therapy Visit was "clinical cure" or "clinical improvement," the patient was instructed to return for a Follow-Up Visit (7 to 14 days posttreatment).

Clinical Reviewer's Note: *These are more accurately termed the discontinuation criteria. The applicant used these criteria when determining patient outcome.*

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Endpoints Defined (Clinical and Microbiological)

The schedule of visits, examinations and evaluations for the patients in this study is shown in Table 26.

Table 26. Study Schematic

Study Procedure	Pretreatment	During Treatment	Posttreatment**		Unscheduled Visit
	Pre-Therapy Visit Study Day 1*	Telephone Contact On-Therapy Visit+ Study Day 3 to 5	Post-Therapy Visit (Within 48 hours after last dose)	Follow-Up Visit (7 to 14 days after last dose)	
Informed Consent	X				
Medical History	X				
Physical Examination	X		X	X	X#
Signs/Symptoms	X	X	X	X	X
Vital Signs	X	X	X	X	X#
Infection Status & Clinical Condition	X				
Skin Infection Site Culture	X	X#	X@	X@	X@#
Laboratory Tests	X	X	X		X#
Dispense Medication	X				
Evaluate Study Drug Compliance		X	X		
Adverse Event Assessment		X	X	X	X
Assess Clinical Response to Therapy			X	X	

* Study Day 1 was the day the first dose was administered.

** Patients who were prematurely discontinued from the study drug therapy were to complete Post-Therapy and Follow-Up Visit evaluations. Patients who were clinical failures were not required to return for the Follow-Up Visit.

@ If culturable material was available.

+ Telephone contact to assess patient's status and schedule the On-Therapy Visit if clinically indicated. If an On-Therapy Visit was clinically indicated, all procedures were to be performed.

If clinically indicated.

Each patient had a baseline evaluation within 48 hours prior to the initiation of therapy. This included a medical history, a physical examination, a clinical assessment of signs and symptoms (classified as absent, mild, moderate, or severe at each visit), specimen collection from the SSSI site, and clinical laboratory tests.

Clinical Endpoints:

The primary efficacy endpoints used to summarize clinical and microbiologic outcomes at the Post-Therapy and Follow-Up Visits included the clinical cure rate, the pathogen eradication rate, and the patient microbiologic cure rate. These endpoints are defined as follows:

> The Clinical Cure Rate - The percentage of patients who had a clinical response of "Cure."
>
> The Pathogen Eradication Rate - The percentage of pathogens that were eradicated for each pretreatment causative skin pathogen and combined over all pretreatment causative skin pathogens.
>
> The Patient Microbiologic Cure Rate - The percentage of patients with pretreatment causative skin pathogens who showed eradication of all pretreatment causative skin pathogens.

The secondary endpoint involved changes from the Pre-Therapy Visit to the Post-Therapy and Follow-Up Visits in each clinical sign/symptom which were summarized by treatment group. Pairwise comparisons of the treatment groups were made with respect to the percentage of patients who demonstrated either resolution (defined as the absence of a symptom at the Post-Therapy or Follow-Up Visit that was present at baseline) or improvement (defined as a decrease in symptom severity from baseline to the Post-Therapy or Follow-Up Visit) in the sign/symptom among the patients presenting with the sign/symptom using Fisher's exact test. Only patients with an evaluation at both baseline and at the Post-Therapy or Follow-Up Visit were included in the analysis.

Clinical Response Definitions:

At the Post-Therapy and Follow-Up Visits, the investigator compared the clinical signs and symptoms with those obtained at the Pre-Therapy Visit, using the following definitions per protocol. Microbiologic results were not considered when assigning the clinical response to therapy.

> Clinical Cure - The pretreatment signs and symptoms of the infection resolved.
>
> Clinical Improvement - The pretreatment signs and symptoms of the infection improved.
>
> Clinical Failure - (Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection did not improve or worsened.

Clinical Relapse - (Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved at the Post-Therapy Visit and worsened or reappeared during the Follow-Up period.

In order to analyze the data according to the July 1998 FDA draft guidelines for anti-infective studies, all clinical responses of "Clinical Improvement" were reassessed by the applicant as either "Clinical Cure" or "Clinical Failure" based on the following definitions. These reassessed clinical responses are used in the efficacy analyses.

Clinical Cure - The pretreatment signs and symptoms of the infection resolved or improved without the need for additional antimicrobial therapy for the treatment of the skin infection.

Clinical Failure - (Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection improved with the need for additional antimicrobial therapy for treatment of skin infection, did not improve, or worsened.

Clinical Relapse - (Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved without the need for additional antimicrobial therapy at the Post-Therapy Visit and worsened or reappeared during the Follow-Up period.

Indeterminate - Clinical response to therapy could not be determined.

Clinically Evaluable Patients:

The following criteria were to have been satisfied for a patient to be considered evaluable for the clinical efficacy analyses:

- The patient's pretreatment (within 4 days prior to the start of study medication) signs and symptoms included at least two of the following: pain, tenderness, swelling, erythema, associated warmth, purulent drainage/discharge, induration, regional lymph node swelling, and regional lymph node tenderness.
- The patient had an appropriate diagnosis of uncomplicated skin or skin structure infection (thermal injury and scalp or nail bed infections were excluded).
- The patient took at least 80% of the scheduled medication. If the patient was considered to be a clinical failure, the patient was still evaluable if he/she had received at least 2 consecutive days of study drug therapy.
- For patients who had a causative skin pathogen isolated pretherapy, no more than one dose of another systemic antimicrobial agent that was known to have activity against the pretherapy causative skin pathogen was taken during the period from the start of study drug to the

Follow-Up Visit (at least 5 days after the end of treatment), unless the patient was considered a study treatment failure.

- For patients who did not have a causative skin pathogen isolated pretherapy, no more than one dose of another systemic antimicrobial agent that was known to have activity against pathogens that cause skin infections was taken during the period from 1 week prior to the start of study drug to the Follow-Up Visit (at least 5 days after the end of treatment), unless the patient was considered a study treatment failure.

- The study treatment blind was not broken prior to a clinical evaluation.

- In order to be considered clinically evaluable at the Post-Therapy Visit (2 days before to 4 days after the end of treatment), a clinical evaluation was made at the Post-Therapy Visit.

- In order to be considered clinically evaluable at the Follow-Up Visit (at least 5 days after the end of treatment), a clinical evaluation was made at the Follow-Up Visit, unless the patient was a "clinical failure" at the Post-Therapy Visit in which case the patient was also considered to be a "clinical failure" at the Follow-Up Visit.

A patient who received additional antimicrobials for the current infection or had incision and drainage performed during treatment, prior to a given visit was considered clinically evaluable for that and subsequent visits if the patient received at least 2 consecutive days of study drug; the patient was considered a "clinical failure" at that and subsequent visits. If a patient prematurely discontinued from study drug therapy due to lack of efficacy or due to an adverse event considered possibly, probably, or definitely related to study drug, a clinical response of "clinical failure" was assigned, and the patient was considered clinically evaluable at that and subsequent visits.

Microbiological endpoints:

Specimens were collected for culture and susceptibility testing at baseline, On-Therapy when indicated, Post-Therapy, and Follow-Up, if material was available. Acceptable culture sources included a swab of the infected lesion, discharge/drainage, blister fluid, or needle aspiration of abscesses or the leading edge of cellulitis. All isolated bacteria suspected of being pathogens were identified to genus and species.

All isolates were tested for susceptibility to cefditoren and cefuroxime axetil by agar dilution and disk diffusion for routine pathogens. Susceptibility results for S. aureus were also assessed by penicillinase production and oxacillin and/or penicillin resistance. Test procedures as well as minimum inhibitory concentration (MIC) and zone diameter standards conformed with National Committee for Clinical Laboratory Standards (NCCLS) guidelines.

Microbiological Response by Pathogen:

Microbiologic response to therapy was assigned at the Post-Therapy and Follow-Up Visits based on the culture results. Response was assigned for each pathogen identified at pretreatment.

Eradication - Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available.

Recurrence - (Applicable for the Follow-Up Visit only) Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available at the Post-Therapy Visit with reappearance of the same pathogen during the Follow-Up period.

Reinfection - Presence of a new pathogen.

Indeterminate - Microbiologic response to therapy could not be assigned.

Microbiologically Evaluable Patients:

The following criteria were to have been satisfied for a patient to be considered evaluable for microbiologic efficacy analyses:

- The patient was clinically evaluable.
- The pretreatment skin infection specimen for culture was obtained within 4 days prior to initiation of study drug therapy and at least one target pathogen (i.e., *S. aureus* and *S. pyogenes*) or other causative skin pathogen was isolated.
- In order to be considered microbiologically evaluable at the Post-Therapy Visit (2 days before to 4 days after the end of treatment), a specimen of skin infection site for routine bacterial culture was obtained or no culturable material was available at the Post-Therapy Visit.
- In order to be considered microbiologically evaluable at the Follow-Up Visit (at least 5 days after the end of treatment), a specimen of skin infection site for routine bacterial culture was obtained or no culturable material was available at the Follow-Up Visit.

A patient who had a microbiologic response of "persistence" at the Post-Therapy Visit was also considered to have a microbiologic response of "persistence" at the Follow-Up Visit if the patient's clinical signs and symptoms were not improving and were indicative of persistent infection or if no Follow-Up Visit evaluation was performed.
A patient who received additional antimicrobials for the current infection or had incision and drainage performed during treatment, prior to a given visit was considered microbiologically evaluable for that and subsequent visits if the patient received at least 2 consecutive days of study drug; a microbiologic response of "persistence" was assigned at that and subsequent visits. If a patient prematurely discontinued from study drug therapy due to lack of efficacy or due to an adverse event considered possibly, probably, or definitely related to study drug, a microbiologic response of "persistence" was assigned; the patient was considered microbiologically evaluable at that and subsequent visits.

Clinical Reviewer's Note: *An evaluable data set was analyzed by the applicant for both the primary and secondary endpoints, and an intent-to-treat (ITT) data set was analyzed for the primary efficacy endpoints. The results for the intent-to-treat population were similar to those in the evaluable patient population. A comparison of the results between the evaluable patients and the ITT patients can be found in the Integrated Summary of Effectiveness.*

The reviewer accepts the applicant's definitions for these endpoints which are very similar to those specified by the DAIDP in its draft guidance for industry document.

Statistical Considerations:

Sample Size: This study was designed to use two-tailed 95% confidence intervals (CI) to assess the equivalence of response rates from evaluable patients who were treated with cefditoren or cefuroxime. It was determined that a sample size of 140 evaluable patients per treatment group would have at least 80% power to meet the criteria that the absolute value of the lower bound of a two-sided 95% confidence interval for the difference in clinical success rates between the cefditoren 400 mg BID treatment group and the cefadroxil monohydrate 500 mg BID treatment group does not exceed 10%. This calculation assumed that the true clinical success rates of both treatment groups was 90%. Assuming an evaluability rate of at least 50%, it was calculated that approximately 840 patients were needed for enrollment to obtain 420 evaluable patients (140 per treatment group).

Methods: Statistical tests used in the analysis of the data were two-tailed at the 0.05 significance level. The primary comparison for efficacy endpoints was between the CDTR-PI 400 mg treatment group and the CXM-AX treatment group; however, all pairwise comparisons were performed for all efficacy and safety analyses. All analyses were performed using SAS®, Version 6.12 [redacted] All p-values were rounded to three decimal places.

Demographic and baseline characteristics were analyzed to assess the comparability of the treatment groups provided by randomization. The quantitative demographic variables, age, height and weight, were analyzed for differences among the treatment groups using a one-way analysis of variance (ANOVA) with treatment group as the factor. The categorical demographic variables, gender and race, were analyzed for differences among the treatment using the chi-square test; the protocol-specified Fisher's exact test was not used due to the prohibitive computational time required for this test.

The baseline characteristics of diagnosis, smoking status, and alcohol consumption were analyzed for differences among the treatment groups by a chi-square test. The baseline characteristics of infection status and clinical condition, and severity of pretreatment clinical signs and symptoms were compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

The primary efficacy endpoints of clinical cure rate, pathogen eradication rate, and patient microbiologic cure rate were summarized by treatment group and analyzed with Fisher's exact test to perform pairwise comparisons of the treatment groups at the Post-Therapy Visit and at the Follow-Up Visit.

Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were also calculated for the difference between each pair of treatment groups for the clinical cure rate and patient microbiologic cure rate. Criteria developed by the FDA require that the absolute value of the lower bound of the 95% confidence interval for the difference between two treatment groups in cure rates not exceed the clinically specified boundary for establishing efficacy equivalence.

The clinical cure rate and patient microbiologic cure rate were also summarized by such factors as age, race, gender, diagnosis, adjunctive therapy use, infection status, clinical condition, smoking status, alcohol use, compliance, treatment duration, and weight. Investigator by treatment interaction was tested using logistic regression. Investigative sites enrolling fewer than 6 patients were combined in this analysis. The Cochran-Mantel-Haenszel test was used as a supportive analysis to assess treatment group differences with the other factors as strata. The Breslow-Day test was used to assess the homogeneity of treatment group differences across the strata.

Study Results

Demographics – Evaluability

There were 63 different investigators who enrolled a total of 857 patients in this study. The two cefditoren arms consisted of 291 patients in the 200 mg group and 283 patients in the 400 mg group. There were 283 patients enrolled in the group to receive 250 mg of cefuroxime axetil BID. The following table shows the number of patients in each of the treatment arms enrolled by each investigator.

Table 27. Distribution of All Enrolled Patients by Investigator

Investigator	Site	Treatment Group CDTR-PI 200 mg	CDTR-PI 400 mg	CFDX-MN 500 mg
Allina	Santa Barbara, CA	8	7	7
Anthony	San Diego, CA	5	5	4
Arno	East Brunswick, NJ	2	1	2
Balin	Media, PA	24	24	24
Barkoff	Albuquerque, NM	0	1	0
Benz	Cedar Rapids, IA	2	2	2
Bettis	Edmonds, WA	5	5	5
Beutner	Vallejo, CA	1	2	1
Bock	Harleyville, PA	5	5	5
Brandon	San Diego, CA	3	3	3
Bruya	Spokane, WA	10	10	11
Bucko	Albuquerque, NM	5	5	4
Carter	Austin, TX	1	1	1
Christensen	Salt Lake City, UT	4	4	4
Daniel	Camden, AR	2	2	3
Davis	San Antonio, TX	4	5	5
Dominguez	El Cajon, CA	2	1	2
Ervin	Kansas City, MO	2	1	2
Ferraro	Bridgewater, NJ	4	4	4
Funicella	Austin, TX	2	2	2
Glinkowski	Houston, TX	3	2	3
Gutierrez	San Antonio, TX	3	1	1
Guzzetta	Clovis, CA	4	4	4
Hassman, D	San Diego, CA	11	10	12
Hassman, H	San Diego, CA	8	9	8
Hassman, M	Berlin, NJ	6	6	6
Hecker	New York, NY	3	4	3
Henry	Salt Lake City, UT	7	7	7
Hogan	Shreveport, LA	2	2	1
Jacobs	Bend, OR	2	2	2
Kaplan	La Jolla, CA	3	3	3
Kerr	Santa Rosa, CA	2	1	2
Lewis	St. Louis, MO	0	1	0
Lipetz	Spring Valley, CA	1	2	1
Macek	Elkins Park, PA	6	7	6
Maloney	Denver, CO	4	4	4
Marbury	Orlando, FL	4	4	4
Miller, D	Morrisville, PA	2	2	2
Miller, R	Tampa, FL	1	1	0
Morman	Rutherford, NJ	1	1	1
Myers	New Port Richey, FL	1	0	0
Nett	San Antonio, TX	11	10	11
Newcomb	Birmingham, AL	6	6	5
Ong	Oxon Hill, MD	2	1	1
Orchard	Boise, ID	4	3	4
Page	Tempe, AZ	6	5	5

Table 27. Distribution of All Enrolled Patients by Investigator (continued)

Investigator	Site	Treatment Group CDTR-PI 200 mg	CDTR-PI 400 mg	CFDX-MN 500 mg
Peterson	Houston, TX	2	1	2
Post	Highlands Ranch, CO	3	4	3
Radbill	Bensalem, PA	5	4	4
Razzetti	Deland, FL	1	1	1
Rhudy	Salt Lake City, UT	5	6	5
Riffer	Phoenix, AZ	4	5	4
Rosemore	Birmingham, AL	6	7	6
Ruoff	Kalamazoo, MI	7	7	7
Salazar	San Antonio, TX	3	4	4
Schenkel	Easton, PA	1	1	2
Schupbach	Charlotte, NC	0	1	2
Shah	Holmdel, NJ	6	6	5
Soiferman	Philadelphia, PA	5	4	5
Sperling	Fountain Valley, CA	6	5	5
Suchyta	Salt Lake City, UT	6	6	5
Sussman	Landsdale, PA	4	4	3
Tashjian	Fresno, CA	6	6	6
Teguh	San Diego, CA	9	9	8
Tomlinson	Wichita Falls, TX	2	1	2
Upchurch	Birmingham, AL	0	1	1
Wade	Salt Lake City, UT	1	2	2
Wenzel	Wellesley Hills, MA	0	1	1
Widman	Sunnyvale, CA	2	3	3
	TOTAL	**278**	**277**	**273**

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate

Patient Demographics: The patient demographics for all patients according to the sponsor are summarized in the following table.

Clinical Reviewer's Note: *The study arms (cefditoren – CDTR-PI – 200 mg BID; cefditoren – CDTR-PI – 400 mg BID; and cefuroxime – CXM-AX – 250 mg BID) appear to be balanced with regard to gender, race, age, and physical characteristics.*

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Table 28. Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CFDX-MN 500 mg BID	P-value[a]
Total Treated	278	277	273	
Gender				0.848
Female	138 (50%)	133 (48%)	129 (47%)	
Male	140 (50%)	144 (52%)	144 (53%)	
Race[b]				0.218
Caucasian	224 (81%)	221 (80%)	217 (79%)	
Hispanic	28 (10%)	37 (13%)	27 (10%)	
Black	20 (7%)	10 (4%)	19 (7%)	
Asian	4 (1%)	2 (1%)	4 (1%)	
Other	2 (1%)	7 (3%)	6 (2%)	
Age (years)[c]				0.268
<45	168 (60%)	178 (64%)	175 (64%)	
45 - 65	75 (27%)	72 (26%)	71 (26%)	
>65	35 (13%)	27 (10%)	27 (10%)	
Mean (SD)	42.6 (16.7)	40.7 (16.5)	40.6 (16.8)	
Range	12 - 95	12 - 85	13 - 93	
Weight (pounds)[c]	N=277	N=277	N=271	0.644
<135	40 (14%)	37 (13%)	35 (13%)	
135 - 165	76 (27%)	73 (26%)	84 (31%)	
166 - 195	80 (29%)	85 (31%)	71 (26%)	
>195	81 (29%)	82 (30%)	81 (30%)	
Missing	1 (<1%)	0 (0%)	2 (1%)	
Mean (SD)	180.1 (43.6)	181.2 (49.7)	177.7 (42.0)	
Range	110 - 340	85 - 401	85 - 355	
Height (inches)[c]	N=277	N=277	N=270	0.705
Mean (SD)	67.1 (4.0)	67.1 (4.3)	67.3 (4.2)	
Range	53 - 78	50 - 79	54 - 79	

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; SD = standard deviation

[a] P-values are from Chi-square test (two-tailed) for gender and race, and a one-way analysis of variance using treatment as the factor for age, weight, and height.

[b] P-value from Chi-square test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Baseline Characteristics (Diagnoses): Baseline characteristics of the three treatment groups according to the sponsor were similar for all patients, with no statistically significant differences. The most common diagnoses were cellulitis (25% of patients), wound infection (24%), folliculitis (13%), and simple abscess (13%). The majority of patients had a moderate infection (66%) and were considered to be in good clinical condition (77%). Baseline characteristics of evaluable patients were similar to those of all patients. Table 29 summarizes the baseline characteristics for all patients by treatment group.

Table 29. Summary of Diagnoses and Baseline Characteristics (All Patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group: CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CFDX-MN 500 mg BID	P-value[a]
Total Treated	278	277	273	
Diagnosis				0.481
Cellulitis	70 (25%)	60 (22%)	73 (27%)	
Wound infection	70 (25%)	64 (23%)	68 (25%)	
Folliculitis	34 (12%)	42 (15%)	31 (11%)	
Simple abscess	37 (13%)	28 (10%)	39 (14%)	
Infected sebaceous cyst	23 (8%)	32 (12%)	26 (10%)	
Impetigo	27 (10%)	25 (9%)	22 (8%)	
Furunculosis	6 (2%)	17 (6%)	10 (4%)	
Other (erysipelas, carbunculosis, etc.)	11 (4%)	9 (3%)	4 (1%)	
Infection Status				0.418
Mild	79 (28%)	79 (29%)	87 (32%)	
Moderate	185 (67%)	184 (66%)	177 (65%)	
Severe	14 (5%)	14 (5%)	9 (3%)	
Clinical Condition				0.262
Good	204 (73%)	217 (78%)	216 (79%)	
Fair	73 (26%)	58 (21%)	56 (21%)	
Poor	1 (<1%)	2 (1%)	1 (<1%)	
Smoking Status				0.118
Non-smoker	136 (49%)	160 (58%)	158 (58%)	
Smoker	98 (35%)	85 (31%)	87 (32%)	
Ex-smoker	44 (16%)	32 (12%)	28 (10%)	
Alcohol Use				0.755
Non-drinker	121 (44%)	125 (45%)	125 (46%)	
Drinker	138 (50%)	140 (51%)	134 (49%)	
Ex-drinker	19 (7%)	12 (4%)	14 (5%)	

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate.

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

Clinical Reviewer's Note: *The various types of skin and skin structure infections studied are acceptable according to the FDA guidelines.*

Drug Administration: The distribution for the duration of therapy for all patients according to the sponsor is provided in the table below.

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Table 30. Duration of Treatment and Study Drug Compliance (Evaluable Patients)

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CFDX-MN 500 mg BID		P-value[a]
Total Treated	258		259		248		
Treatment Duration (days)							0.693
<4	4	(2%)	7	(3%)	7	(3%)	
4 – 7	5	(2%)	9	(3%)	6	(2%)	
8 – 10	182	(71%)	158	(61%)	163	(66%)	
>10	67	(26%)	85	(33%)	72	(29%)	
Mean (SD)							
Min – Max	2 - 12		1 - 12		1 - 12		
Compliance[b] (percentage)							0.225
<80	10	(4%)	17	(7%)	13	(5%)	
80 – 90	15	(6%)	15	(6%)	8	(3%)	
>90	233	(90%)	227	(88%)	227	(92%)	
Mean (SD)							
Min – Max	15 - 100		5 - 100		5 - 100		

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; SD = standard deviation

[a] P-value for F-test for testing equality of treatment means.

[b] For patients who did not return study drug containers, compliance was calculated using the number of days on treatment.

Clinical Reviewer's Note: *The mean patient exposure to cefditoren for the two treatment groups was 10 days, which is the treatment duration proposed in the label. Compliance was >90% for most patients in all three arms of the study.*

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Unevaluable Patients: The following table shows the number of clinically evaluable patients and microbiologically evaluable patients according to the sponsor, along with the various reasons for excluding unevaluable patients in each arm of the study.

Table 31. Disposition of Patients by Data Set

	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CFDX-MN 500 mg BID
All Patients: Randomized and Received Study Drug[a]	278	277	273
Included in Clinically Evaluable Efficacy Analyses:			
Post-Therapy	252	248	244
Follow-Up	258	259	248
Excluded at Post-Therapy:	26	29	29
No clinical response assessed within visit window	15	18	15
Received less than 80% of study drug	3	3	6
Admission criteria not met	3	2	4
Received less than 2 consecutive days of study drug	2	3	1
Lost to follow-up	1	3	1
Pretherapy assessment performed too early	1	0	0
Previously enrolled in a cefditoren study with same indication	0	0	1
Received additional antimicrobials	0	0	1
Received another antimicrobial agent pretreatment	1	0	0
Excluded at Follow-Up:	20	18	25
No clinical response assessed with visit window	6	4	7
Received additional antimicrobials	4	3	5
Received less than 80% of study drug	2	2	6
Admission criteria not met	3	2	4
Received less than 2 consecutive days of study drug	2	3	1
Lost to follow-up	1	3	1
Misdiagnosis	0	1	0
Pretherapy assessment performed too early	1	0	0
Previously enrolled in a cefditoren study with same indication	0	0	1
Received another antimicrobial agent pretreatment	1	0	0
Included in Microbiologically Evaluable Efficacy Analyses:			
Post-Therapy	121	124	115
Follow-Up	120	127	116
Excluded at Post-Therapy:	157	153	158
No causative skin pathogen isolated pretreatment	147	140	141
No culture obtained within visit window	4	7	11
Admission criteria not met	1	1	2
Received less than 80% of study drug	2	1	2
Lost to follow-up	1	2	0
Culture results could not be confirmed	1	1	0
Received less than 2 consecutive days of study drug	0	1	1
Pretherapy assessment performed too early	1	0	0
Received additional antimicrobials	0	0	1
Excluded at Follow-Up:	158	150	157
No causative skin pathogen isolated pretreatment	147	140	141
No culture obtained within visit window	4	4	7
Received additional antimicrobials	2	1	4
Admission criteria not met	1	1	2
Received less than 80% of study drug	1	0	2
Lost to follow-up	1	2	0
Culture results could not be confirmed	1	1	0
Received less than 2 consecutive days of study drug	0	1	1
Pretherapy assessment performed too early	1	0	0

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate

[a] All data from site #13057 were excluded; see Section 6.0.

Clinical Reviewer's Note: *Of the 278 patients enrolled in the 200 mg cefditoren group, 120 (43%) patients were evaluable for both a clinical and microbiological analysis. In the 400 mg cefditoren group, 127 (46%) of the 277 enrolled patients were evaluable for both analyses. For the cefuroxime group, 116/273 (42%) were evaluable. The groups appear to be comparable.*

Efficacy

Clinical efficacy: The primary clinical endpoint of clinical cure rate and secondary efficacy endpoint of changes in clinical signs and symptoms from the Pre-Therapy Visit were assessed for patients who were clinically evaluable. The clinical cure rates for the evaluable patients from the three treatment groups at the Post-Therapy and Follow-Up visits are shown in the following tables.

Table 32. Clinical Response at the Post-Therapy Visit (Evaluable Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	224/252	(89%)	219/248	(88%)	220/244	(90%)
Failure	28/252	(11%)	29/248	(12%)	24/244	(10%)

Comparison of Cure Rates	P-value[a]	95% CI for Difference in Cure Rate[b]
CDTR-PI 200 mg vs CFDX-MN	0.663	[-6.7, 4.1]
CDTR-PI 400 mg vs CFDX-MN	0.562	[-7.3, 3.6]
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.889	[-5.0, 6.2]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Table 33. Clinical Response at the Follow-Up Visit (Evaluable Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	220/258	(85%)	211/259	(81%)	211/248	(85%)
Failure	38/258	(15%)	48/259	(19%)	37/248	(15%)

Comparison of Cure Rates	P-value[a]	95% CI for Difference in Cure Rate[b]
CDTR-PI 200 mg vs CFDX-MN	>0.999	[-6.0, 6.4]
CDTR-PI 400 mg vs CFDX-MN	0.287	[-10.1, 2.9]
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.288	[-2.6, 10.2]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Clinical Reviewer's Note: *A 97.5% CI should have been used for the multiple comparisons between the three arms of the study to determine any differences in clinical cure rates. This correction was made subsequently by the applicant and in an FDA statistical review by Thambam Valappil, Ph.D. Both the applicant's re-analysis and Dr. Valappil's analysis showed the drugs to be comparable within the 97.5% confidence interval for the difference in clinical cure rates. See Dr. Valappil's review of NDA 21-222 for details.*

Microbiologically Evaluable Patients: This group consists of clinically evaluable patients who had a skin pathogen isolated at the pre-therapy visit and were evaluated at both the Post-Therapy and Follow-Up visits. The primary microbiological endpoints of microbiologic cure rate and pathogen eradication rates were assessed and the results are shown in the following tables for the Post-Therapy and Follow-Up visits.

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Table 34. Microbiologic Response at the Post-Therapy Visit (Evaluable Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	106/121	(88%)	106/124	(85%)	94/115	(82%)
Mixed[a]	0/121	(0%)	2/124	(2%)	2/115	(2%)
Failure	15/121	(12%)	16/124	(13%)	19/115	(17%)

Comparison of Cure Rates	P-value[b]	95% CI for Difference in Cure Rate[c]
CDTR-PI 200 mg vs CFDX-MN	0.277	[-3.3, 15.0]
CDTR-PI 400 mg vs CFDX-MN	0.486	[-5.7, 13.1]
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.709	[-6.4, 10.7]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] Eradication of some but not all of the pretreatment causative skin pathogens.
[b] P-value for comparison between treatment groups using Fisher's exact test.
[c] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

Table 35. Microbiologic Response at the Follow-Up Visit (Evaluable Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	101/120	(84%)	101/127	(80%)	90/116	(78%)
Mixed[a]	0/120	(0%)	2/127	(2%)	2/116	(2%)
Failure	19/120	(16%)	24/127	(19%)	24/116	(21%)

Comparison of Cure Rates	P-value[b]	95% CI for Difference in Cure Rate[c]
CDTR-PI 200 mg vs CFDX-MN	0.246	[-3.4, 16.6]
CDTR-PI 400 mg vs CFDX-MN	0.756	[-8.4, 12.3]
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.410	[-4.9, 14.2]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] Eradication of some but not all of the pretreatment causative skin pathogens.
[b] P-value for comparison between treatment groups using Fisher's exact test.
[c] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

The cure rates for the microbiologically evaluable patients were 101/120 (84%)for the 200 mg cefditoren group, 101/127 (80%) for the 400 mg cefditoren group, and 90/116 (78%) for the cefadroxil group.

Clinical cure rates by Diagnosis: The sponsor was requested to provide data showing the clinical cure rates for clinically evaluable patients according to the baseline diagnosis. The following tables show the results at the Post-Therapy and Follow-Up visits.

Clinical Reviewer's Note: *The cure rates for the study drug for all skin infections appear to be comparable to the cure rates for the comparator drug.*

Table 36. CLINICAL CURE RATE BY BASELINE DIAGNOSIS AT THE POST- THERAPY VISIT
EVALUABLE PATIENTS
CEF- 97- 011

BASELINE DIAGNOSIS	CEFDITOREN PIVOXIL == 200 MG BID == n/N	PCT	CEFDITOREN PIVOXIL == 400 MG BID == n/N	PCT	CEFADROXIL MONOHYDRATE == 500 MG BID == n/N	PCT
CELLULITUS	53/67	79%	48/54	89%	56/64	88%
FOLLICULITIS	28/29	97%	34/38	89%	28/30	93%
FURUNCULOSIS	4/5	80%	17/17	100%	7/8	88%
SIMPLE ABSCESS	31/34	91%	20/22	91%	30/33	91%
IMPETIGO	24/24	100%	19/23	83%	17/19	89%
INFECTED SEBACEOUS CYST	19/21	90%	26/31	84%	22/25	88%
WOUND INFECTION	57/62	92%	50/58	86%	57/61	93%
ERYSIPELAS	1/1	100%	0/0		0/0	
CARBUNCULOSIS	4/4	100%	1/1	100%	2/2	100%
OTHER	3/5	60%	4/4	100%	1/2	50%
ACROSS DIAGNOSIS	224/252	89%	219/248	88%	220/244	90%

n/ N = NUMBER OF PATIENTS CURED/ TOTAL NUMBER OF PATIENTS

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Table 37. CLINICAL CURE RATE BY BASELINE DIAGNOSIS AT THE FOLLOW- UP VISIT
EVALUABLE PATIENTS
CEF- 97- 011

BASELINE DIAGNOSIS	CEFDITOREN PIVOXIL == 200 MG BID == n/ N	PCT	CEFDITOREN PIVOXIL == 400 MG BID == n/ N	PCT	CEFADROXIL MONOHYDRATE == 500 MG BID == n/ N	PCT
CELLULITUS	53/67	79%	50/56	89%	55/66	83%
FOLLICULITIS	25/31	81%	30/38	79%	21/29	72%
FURUNCULOSIS	4/5	80%	14/17	82%	8/9	89%
SIMPLE ABSCESS	28/33	85%	22/25	88%	28/33	85%
IMPETIGO	24/26	92%	17/25	68%	17/19	89%
INFECTED SEBACEOUS CYST	18/22	82%	25/32	78%	23/26	88%
WOUND INFECTION	60/64	94%	50/61	82%	56/62	90%
ERYSIPELAS	1/1	100%	0/0		0/0	
CARBUNCULOSIS	4/4	100%	1/1	100%	2/2	100%
OTHER	3/5	60%	2/4	50%	1/2	50%
ACROSS DIAGNOSIS	220/258	85%	211/259	81%	211/248	85%

n/ N = NUMBER OF PATIENTS CURED/ TOTAL NUMBER OF PATIENTS

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Microbiology

Table 38 shows the eradication rates for the applicant's proposed pathogens at the Post-Therapy visit for all three treatment groups.

Table 38. Eradication Rates for Causative Skin Pathogens at the Post-Therapy Visit (Evaluable Patients)

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
OVERALL	140/155	(90%)	141/161	(88%)	125/154	(81%)
S. aureus	66/77	(86%)	73/87	(84%)	68/83	(82%)
S. pyogenes	10/11	(91%)	6/6	(100%)	3/3	(100%)
P. magnus	15/16	(94%)	15/15	(100%)	8/11	(73%)
P. asaccharolyticus	6/6	(100%)	4/4	(100%)	7/8	(88%)
E. faecalis	6/6	(100%)	4/4	(100%)	7/8	(88%)
P. aeruginosa	6/7	(86%)	3/4	(75%)	1/4	(25%)
S. agalactiae	2/2	(100%)	4/5	(80%)	7/7	(100%)
Bacteroides spp.	5/5	(100%)	6/6	(100%)	6/9	(67%)
Enterobacter spp.	4/4	(100%)	6/6	(100%)	2/3	(67%)

Comparison of Overall Eradication Rates	P-value[a]
CDTR-PI 200 mg vs CFDX-MN	0.023*
CDTR-PI 400 mg vs CFDX-MN	0.123
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.477

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] P-value for comparison between treatment groups using Fisher's exact test.
* Indicates statistical significance at the $p \leq 0.05$ level.

In the 200 mg cefditoren group, 140 of 155 (90%) isolates were eradicated overall, while 141 of 161 (88%) isolates in the 400 mg cefditoren group were eradicated. In the cefadroxil group, 125 of 154 (81%) isolates were eradicated at the Post-Therapy visit.

Clinical Reviewer's Note: *Since the target organisms for this indication are S. aureus and S. pyogenes, it is necessary to compare the effects of the study drug on these species. In the 200 mg cefditoren group, 66 of the 77 S. aureus isolates were eradicated for an 86% cure rate. In the 400 mg cefditoren group, 73 of the 87 (84%) isolates of S. aureus were eradicated, while in the cefadroxil group, 68 of 83 (82%) isolates were eradicated. Both doses of cefditoren performed better than the comparator drug, with the 200 mg cefditoren group having the highest eradication rate at 86%. For S. pyogenes, both the 400 cefditoren group and the cefadroxil group had 100% cure rates with six isolates and three isolates, respectively. The 200 mg cefditoren group had a 91% eradication rate (10/11). The number of S. pyogenes isolates was small across all three arms of the study; thus, no conclusions can be made regarding the comparisons of the drugs.*

Table 39 shows the eradication rates for all skin pathogens at the Follow-up visit for all evaluable patients.

Table 39. Eradication Rates for Causative Skin Pathogens at the Follow-Up Visit (Evaluable Patients)

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
OVERALL	132/151	(87%)	135/165	(82%)	121/158	(77%)
S. aureus	64/77	(83%)	69/88	(78%)	70/86	(81%)
S. pyogenes	10/11	(91%)	5/5	(100%)	2/2	(100%)
P. magnus	13/14	(93%)	14/14	(100%)	4/10	(40%)
P. asaccharolyticus	5/5	(100%)	4/4	(100%)	6/7	(86%)
E. faecalis	6/6	(100%)	4/4	(100%)	7/8	(88%)
P. aeruginosa	6/8	(75%)	3/4	(75%)	1/4	(25%)
S. agalactiae	2/2	(100%)	3/6	(50%)	6/7	(86%)
Bacteroides spp.	4/4	(100%)	6/6	(100%)	6/10	(60%)
Enterobacter spp.	5/5	(100%)	6/6	(100%)	2/3	(67%)

Comparison of Overall Eradication Rates	P-value[a]
CDTR-PI 200 mg vs CFDX-MN	0.018*
CDTR-PI 400 mg vs CFDX-MN	0.273
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.213

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] P-value for comparison between treatment groups using Fisher's exact test.
* Indicates statistical significance at the $p \leq 0.05$ level.

The overall eradication rates in the above table show the 200 mg dose of cefditoren to be the most effective at 87% (132/151), followed by the 400 mg dose at 82% (135/165), and the cefadroxil dose at 77% (121/158).

Clinical Reviewer's Note: *The 200 mg cefditoren dose was the most effective at eradicating S. aureus at an 83% rate, followed by cefadroxil at 81% and the 400 mg cefditoren dose at 78%. It is interesting to note that the lower dose of cefditoren performed better than the higher dose. These data differ from those in the previous study where the higher dose had a higher eradication rate for this pathogen, 87% versus 83%. The number of S. pyogenes isolates in all three treatment arms was very small with all drugs showing good eradication rates.*

Clinical Reviewer's Analysis of Data

The applicant was requested to submit the case report forms with the treatment group blinded for 90 randomized patients, 30 patients from each arm of the study. The 90 case report forms were submitted on April 24, 2000. The FDA analysis of these patient groups for each study was then compared to the applicant's results for these groups.
The results are shown in the following table.

Table 40. Comparison of FDA Review with the Applicant's of the Randomized Patients.

Treatment Group	Applicant's Original Results	FDA's Results
Cefditoren 200 mg group		
Clinical cure rate	24/27 (88.9%)	22/27 (81.5%)
Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*)	9/10 (90.0%)	6/10 (60.0%)
Cefditoren 400 mg group		
Clinical cure rate	20/26 (76.9%)	19/25 (76.0%)
Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*)	5/8 (62.5%)	4/8 (50.0%)
Cefadroxil 500 mg group		
Clinical cure rate	21/28 (75.0%)	20/28 (71.4%)
Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*)	11/13 (84.6%)	10/13 (76.9%)

The clinical cure rates for the three blinded treatment groups as determined by the applicant were as follows: 24/27 (88.9%) for the 200 mg cefditoren group, 20/26 (76.9%) for the 400 mg cefditoren group, and 21/28 (75.0%) for the cefadroxil monohydrate group. In the FDA analysis, the cure rates for these treatment groups were 22/27 (81.5%), 19/25 (76.0%), and 20/28 (71.4%), respectively. In both the applicant and FDA's analysis of these patient groups, the patients receiving the 200-mg dose of cefditoren had a higher cure rate than those receiving the 400-mg dose.

During the comparison of the applicant and FDA's analysis, two major issues developed concerning the differences between the results. As described in study Cef-97-009, the applicant was asked to re-evaluate patients listed as clinical cures and improvements by the investigators based on criteria used by the FDA in its analysis and also, to change the microbiological results to failures for all patients who were clinical failures or clinical relapses.

The applicant completed the re-evaluation of both the investigator-assigned clinical cures and clinical improvements based on their signs/symptoms at the follow-up visit and submitted the results on August 31, 2000. In study Cef-97-011, the clinical cure rates for the three treatment groups after the re-evaluation were as follows: in the 200 mg cefditoren group 205/258 (79%), in the 400 mg cefditoren group 193/259 (75%), and in the 500 mg cefadroxil group 195/248 (79%). The cure rates for the microbiologically evaluable patients were 88/120 (73%), 93/120 (73%), and 84/116 (72%), respectively.

Table 41 shows the clinical cure rates and the patient microbiological cure rates for the three treatment groups found in the initial submission and the results after the applicant's re-evaluation of the data.

Clinical Reviewer's Note: *The re-evaluation of the clinical data by the applicant resulted in a reduction in cure rates for both the clinically evaluable patients and the microbiologically evaluable patients across all three treatment arms. The reductions in cure rates were 6% for all three treatment groups. At each evaluation step, the 200 mg cefditoren dose performed better than the 400 mg cefditoren dose, 79% versus 75% at the last analysis. Cefadroxil also outperformed the higher cefditoren dose 79% to 75%. The cure rates for all three groups were comparable according to the lower bounds of the 95% confidence intervals determined by the applicant.*

For the microbiologically evaluable patients, the reductions in cure rates were 11% for the 200 mg cefditoren group, 7% for the 400 mg cefditoren group, and 6% for the cefadroxil group. The cure rates for the three treatment arms are equivalent according to the 95% CIs for the differences as determined by the applicant.

Microbiology

Table 42 shows the results of the re-analysis of the pathogen eradication data for *S. aureus* and *S. pyogenes*.

Clinical Reviewer's Note: *The re-evaluation of the clinical data resulted in reductions in the eradication rates for the two target pathogens. For S. aureus, the eradication rate in the 200 mg cefditoren group changed from 83% to 74%, in the 400 mg cefditoren group from 78% to 74%, and in the cefadroxil group from 81% to 77%. For S. pyogenes, the eradication rate changed from 91% to 73% in the 200 mg cefditoren group, and from 100% to 60% in the 400 mg cefditoren group. There was no change in the rate for the 500 mg cefadroxil group.*

Table 41. Re-analysis of Clinical and Patient Microbiological Data

Cef-97-011

Treatment Group	Initial Submission 12-28-99	Override of Investigator's Clinical Improvements	Override of Investigator's * Cures & Clinical Improvements
Cefditoren 200 mg group			
Clinical cures	220/258 (85%)	211/258 (82%)	205/258 (79%)
Patient Micro. Cures	101/120 (84%)	92/120 (77%)	88/120 (73%)
Cefditoren 400 mg group			
Clinical cures	211/259 (81%)	194/259 (75%)	193/259 (75%)
Patient Micro. Cures	101/127 (80%)	93/127 (73%)	93/127 (73%)
Cefadroxil 500 mg group			
Clinical cures	211/248 (85%)	197/248 (79%)	195/248 (79%)
Patient Micro. Cures	90/116 (78%)	84/116 (72%)	84/116 (72%)

* Confidence intervals for differences in cure rates between groups

Clinical Response – Cures	P-Values	95% CI for difference
Cefditoren 200mg vs Cefadroxil	0.828	[-6.3, 7.9]
Cefditoren 400mg vs Cefadroxil	0.295	[-11.5, 3.2]
Cefditoren 200mg vs Cefditoren 400mg	0.210	[-2.3, 12.2]
Microbiological Response – Cures		
Cefditoren 200mg vs Cefadroxil	0.885	[-10.4, 12.3]
Cefditoren 400mg vs Cefadroxil	0.886	[-10.4, 12.0]
Cefditoren 200mg vs Cefditoren 400mg	>0.999	[-10.9, 11.1]

Table 42. Re-analysis of the Pathogen Eradication Data

Cef-97-011

Treatment Group	Initial Submission 12-28-99	Override of Investigator's Clinical Improvements	Override of Investigator's Cures & Clinical Improvements
Cefditoren 200 mg group			
S. aureus	64/77 (83%)	60/77 (78%)	57/77 (74%)
S. pyogenes	10/11 (91%)	8/11 (73%)	8/11 (73%)
Cefditoren 400 mg group			
S. aureus	69/88 (78%)	65/88 (74%)	65/88 (74%)
S. pyogenes	5/5 (100%)	3/5 (60%)	3/5 (60%)
Cefadroxil 500 mg group			
S. aureus	70/86 (81%)	66/86 (77%)	66/86 (77%)
S. pyogenes	2/2 (100%)	2/2 (100%)	2/2 (100%)

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Safety

The safety of the study drugs was monitored throughout the study by physical examinations, including vital signs, clinical laboratory tests, and the assessment of adverse events. All patients who received at least one dose of study drug (N=828) were included in the safety analyses.

Adverse Events as reported by the Applicant

The criteria for determining adverse events, treatment related events, and the definitions used to rate the severity of each event are identical to those definitions found in study Cef-97-009.

All Adverse Events

Of the 828 randomized patients who received study drug, 125 patients (45%) in the 200 mg cefditoren group, 124 patients (45%) in the 400 mg cefditoren group, and 100 patients (37%) in the cefadroxil group reported at least one adverse event during treatment. The most commonly reported adverse events during treatment in the 200 mg cefditoren, 400 mg cefditoren, and cefadroxil groups included diarrhea (16%, 21%, and 8%, respectively), nausea (6%, 5%, and 7%, respectively), and headache (6%, 5%, and 6%, respectively). According to the applicant, statistically significant differences were observed between the 200 mg cefditoren and the cefadroxil treatment groups ($p=0.004$) and between the 400 mg cefditoren and the cefadroxil treatment groups ($p<0.001$) in the incidence of diarrhea; no other statistically significant differences were noted between treatment groups for the incidence of any specific adverse event. Table 43 shows the summary of common adverse events experienced by patients in the three treatment groups as determined by the applicant.

Table 43. Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=278)					CDTR-PI 400 mg BID (N=277)					CFDX-MN 500 mg BID (N=273)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	**Mild**	**Mod**	**Sev**	**Total**	**%**	**Mild**	**Mod**	**Sev**	**Total**	**%**	**Mild**	**Mod**	**Sev**	**Total**	**%**
OVERALL[c]				125	45%				124	45%				100	37%
BODY AS A WHOLE				44	16%				47	17%				41	15%
Headache	9	6	1	16	6%	7	6	1	14	5%	9	6	1	16	6%
Abdominal pain	6	4	1	11	4%	6	3	1	10	4%	5	0	2	7	3%
Infection	4	4	1	9	3%	6	1	0	7	3%	5	2	0	7	3%
Asthenia	0	1	1	2	1%	3	2	1	6	2%	3	1	0	4	1%
DIGESTIVE SYSTEM#				66	24%				82	30%				47	17%
Diarrhea$#	23	19	2	44	16%	41	13	4	58	21%	15	4	2	21	8%
Nausea	13	3	0	16	6%	12	1	1	14	5%	12	8	0	20	7%
Dyspepsia	4	2	0	6	2%	3	1	1	5	2%	3	5	1	9	3%
RESPIRATORY SYSTEM				10	4%				7	3%				10	4%
Rhinitis	1	2	0	3	1%	3	2	0	5	2%	1	1	0	2	1%
SKIN AND APPENDAGES				11	4%				8	3%				7	3%
Rash	1	3	1	5	2%	2	0	0	2	1%	1	1	0	2	1%
Pruritus	1	2	0	3	1%	4	1	0	5	2%	1	2	0	3	1%
UROGENITAL SYSTEM (female)[d]				(N=138) 8	6%				(N=133) 5	4%				(N=129) 6	5%
Vaginal Moniliasis[d]	1	3	0	4	3%	2	2	1	5	4%	3	1	0	4	3%
Vaginitis[d]	1	3	0	4	3%	0	0	0	0	0%	0	1	0	1	1%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; Mod = moderate; Sev = severe

$ Statistically significant difference in incidence rate between CDTR-PI 200 mg and CFDX-MN, p≤0.01.

\# Statistically significant difference in incidence rate between CDTR-PI 400 mg and CFDX-MN, p≤0.001.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

Treatment-Related Adverse Events:

Eighty-eight (32%) patients in the cefditoren 200 mg group, 95 (34%) patients in the cefditoren 400 mg group, and 69 (25%) patients in the cefadroxil group reported at least one adverse event during treatment that was considered by the investigator to be possibly, probably, or definitely treatment-related. The most frequently occurring treatment-related adverse events in all three treatment groups were diarrhea and nausea. In the cefditoren 200 mg, cefditoren 400 mg, and cefadroxil groups, diarrhea was reported by 16%, 20%, and 8% of patients, respectively, and nausea was reported by 5%, 5%, and 7% of patients, respectively. In addition, headache was reported by 5% of patients in the cefditoren 400 mg group

The summary of treatment-related adverse events grouped by COSTART term as determined by the applicant is shown in the following table.

Table 44. Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=278)					CDTR-PI 400 mg BID (N=277)					CFDX-MN 500 mg BID (N=273)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c#]				88	32%				95	34%				69	25%
BODY AS A WHOLE				24	9%				25	9%				20	7%
Headache	7	4	0	11	4%	6	6	1	13	5%	5	5	1	11	4%
Abdominal pain	6	4	1	11	4%	5	3	1	9	3%	4	0	1	5	2%
DIGESTIVE SYSTEM[#]				61	22%				76	27%				43	16%
Diarrhea[S#]	23	19	2	44	16%	40	12	3	55	20%	15	4	2	21	8%
Nausea	11	3	0	14	5%	12	1	1	14	5%	10	8	0	18	7%
Dyspepsia	4	2	0	6	2%	3	1	1	5	2%	3	4	1	8	3%
UROGENITAL SYSTEM (female)[d]				(N=138) 7	5%				(N=133) 5	4%				(N=129) 5	4%
Vaginal Moniliasis[d]	1	3	0	4	3%	2	2	1	5	4%	3	1	0	4	3%
Vaginitis[d]	1	2	0	3	2%	0	0	0	0	0%	0	1	0	1	1%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; Mod = moderate; Sev = severe

[S] Statistically significant difference in incidence rate between CDTR-PI 200 mg and CFDX-MN, p≤0.01.

[#] Statistically significant difference in incidence rate between CDTR-PI 400 mg and CFDX-MN, p≤0.05.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

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Table 45. Summary of All Adverse Events Grouped by Body System (During Treatment)

	Number (%) of Patients[a]					
	CDTR-PI 200 mg BID (N=278)		CDTR-PI 400 mg BID (N=277)		CFDX-MN 500 mg BID (N=273)	
Body System						
OVERALL[b]	125	45%	124	45%	100	37%
Body as a Whole	44	16%	47	17%	41	15%
Cardiovascular	3	1%	2	1%	2	1%
Digestive[#]	66	24%	82	30%	47	17%
Hemic and Lymphatic	1	<1%	0	0%	1	<1%
Metabolic and Nutritional Disorders	5	2%	5	2%	1	<1%
Musculoskeletal	1	<1%	1	<1%	1	<1%
Nervous	15	5%	12	4%	10	4%
Respiratory	10	4%	7	3%	10	4%
Skin and Appendages	11	4%	8	3%	7	3%
Special Senses	3	1%	0	0%	1	<1%
Urogenital (excluding female-specific)	2	1%	2	1%	1	<1%
Urogenital[c] (females)	8	6%	5	4%	6	5%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate

[#] Statistically significant difference between CDTR-PI 400 mg and CFDX-MN, p=0.001.

[a] Patients with more than one event within a body system are counted only once in the total for that body system; patients with events in more than one body system are counted only once in the overall total.

[b] Number of patients with one or more adverse events.

[c] Gender-specific body system; percentage given is of females only.

Analysis of Adverse Events

During treatment, the incidences of all adverse events and treatment-related adverse events were 45% and 32%, respectively, in the cefditoren 200 mg group, 45% and 34%, respectively, in the cefditoren 400 mg group, and 37% and 25%, respectively, in the cefadroxil group. The most frequently occurring treatment-related adverse events in all three treatment groups were diarrhea and nausea. In the 200 mg cefditoren, 400 mg cefditoren, and cefadroxil groups, diarrhea was reported by 16%, 20%, and 8%, respectively, and nausea was reported by 5%, 5%, and 7%, respectively. In addition, 5% of patients in the cefditoren 400 mg group reported headache.

Table 46. Summary of Treatment-Related Adverse Events Grouped by Body System (During Treatment)

	Number (%) of Patients[a]					
	CDTR-PI 200 mg BID (N=278)		CDTR-PI 400 mg BID (N=277)		CFDX-MN 500 mg BID (N=273)	
Body System						
OVERALL[b#]	88	32%	95	34%	69	25%
Body as a Whole	24	9%	25	9%	20	7%
Cardiovascular	0	0%	1	<1%	0	0%
Digestive[#]	61	22%	76	27%	43	16%
Hemic and Lymphatic	0	0%	0	0%	1	<1%
Metabolic and Nutritional Disorders	1	<1%	3	1%	0	0%
Nervous	10	4%	7	3%	6	2%
Respiratory	2	1%	0	0%	1	<1%
Skin and Appendages	4	1%	3	1%	4	1%
Special Senses	1	<1%	0	0%	1	<1%
Urogenital (excluding female-specific)	0	0%	1	<1%	1	<1%
Urogenital[c] (females)	7	5%	5	4%	5	4%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate

[#] Statistically significant difference between CDTR-PI 400 mg and CFDX-MN, p≤0.05.

[a] Patients with more than one event within a body system are counted only once in the total for that body system; patients with events in more than one body system are counted only once in the overall total.

[b] Number of patients with one or more adverse events.

[c] Gender-specific body system; percentage given is of females only.

Serious Adverse Events: The definitions for serious adverse events in this study were identical to those described in study Cef-97-009. The following table shows the number of patients who experienced serious adverse events during the study.

Table 47. Patients Who Experienced Serious Adverse Events

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term	SAE Criteria
Patients with Serious Adverse Events in the Cefditoren Pivoxil 200 mg BID Treatment Group						
Riffer 5403#	58/M	4 (0)	39 (35)	Body as a whole	Infection	HOSP
Ruoff 5958#	67/F	3 (0)	5 (2)	Body as a whole	Cellulitis	HOSP
Schenkel 5027	64/F	32 (20)	37 (25)	Cardiovascular	Cerebrovascular accident	HOSP, L-T
		32 (20)	Cont.: 62 (50)	Body as a whole	Infection bacterial	HOSP, L-T
		32 (20)	Cont.: 62 (50)	Cardiovascular	Cardiovascular disorder	HOSP, L-T
Patients with Serious Adverse Events in the Cefditoren Pivoxil 400 mg BID Treatment Group						
Bruya 5787#	53/F	2 (0)	9 (7)	Musculoskeletal	Tenosynovitis	HOSP
Newcomb 5770#	37/M	4 (0)	8 (4)	Body as a whole	Cellulitis	HOSP
Patients with Serious Adverse Events in the Cefadroxil Monohydrate 500 mg BID Treatment Group						
Brandon 5045#	75/F	4	18 (9)	Respiratory	Pneumonia	HOSP
Rosemore 5821	29/F	8	18 (8)	Cardiovascular	Deep thrombophlebitis	HOSP

HOSP = hospitalization; L-T = life-threatening
\# Patient prematurely discontinued from the study.
[a] Days posttreatment are presented in parentheses; Cont. = event continued as of specified day.

Clinical Reviewer's Note: *There were three patients in the 200 mg cefditoren group, two patients in the 400 mg cefditoren group, and two patients in the cefadroxil group who experienced a serious adverse event. These numbers across all treatment arms are not high, considering the number of patients in the study.*

Discontinued Patients: Table 48 is a summary of treatment discontinuations. It shows that eight patients in the 200 mg cefditoren group, 20 patients in the 400 mg cefditoren group, and 10 patients in the cefadroxil group discontinued the study because of adverse events.

Clinical Reviewer's Note: *The high number of patient discontinuations due to adverse events in the 400 mg cefditoren group (20) compared to the number in the 200 mg cefditoren group (8) may be significant. These differences are most likely due to the higher incidence of digestive adverse events, especially diarrhea.*

Table 48. Patients Who Prematurely Discontinued Treatment Due to Adverse Events

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term
Patients Discontinued from the Cefditoren Pivoxil 200 mg BID Treatment Group					
Allina 5514	73/M	2	4 (1)	Skin and appendages	Maculopapular rash
Ervin 5106	41/F	6	25 (18)	Digestive	Diarrhea[b]
		6	25 (18)	Skin and appendages	Pruritus[b]
Henry 5304	48/F	5	11 (3)	Urogenital	Vaginal moniliasis[b]
Maloney 5897	26/M	5	9 (1)	Digestive	Diarrhea[b]
Miller 5038	53/F	2 (0)	3 (1)	Digestive	Dyspepsia[b]
		2 (0)	3 (1)	Urogenital	Vaginitis[b]
Riffer 5403	58/M	4 (0)	39 (35)	Body as a whole	Infection
Ruoff 5552	46/M	3	12 (7)	Body as a whole	Allergic reaction[b]
Teguh 5435	64/M	2	4 (1)	Digestive	Diarrhea[b]
		2	4 (1)	Nervous	Dizziness[b]
Patients Discontinued from the Cefditoren Pivoxil 400 mg BID Treatment Group					
Balin 5144	39/F	4 (0)	6 (2)	Digestive	Diarrhea[b]
Balin 5362	27/F	9 (1)	11 (3)	Body as a whole	Abdominal pain[b]
		9 (1)	11 (3)	Digestive	Diarrhea[b]
		9 (1)	11 (3)	Body as a whole	Fever[b]
Balin 5365	30/F	10 (0)	11 (1)	Body as a whole	Flu syndrome[b]
Balin 5621	60/M	1	[12 hrs]	Body as a whole	Headache[b]
Balin 5624	55/M	2	4 (1)	Metabolic and nutritional	Thirst[b]
Balin 6001	72/M	10 (0)	12 (2)	Cardiovascular	Postural hypotension[b]
Balin 6007	25/F	3	9 (1)	Body as a whole	Headache[b]
Benz 5099	25/F	1 (0)	[3½ hrs]	Nervous	Dizziness[b]
		1 (0)	[3½ hrs]	Digestive	Nausea[b]
Beutner 5181	52/F	2 (0)	3 (1)	Nervous	Nervousness
Bock 5544	27/F	5 (1)	7 (3)	Digestive	Diarrhea[b]
Bruya 5787	53F	1	2 (0)	Digestive	Diarrhea[b]
		1	2 (0)	Digestive	Nausea[b]
		1	2 (0)	Digestive	Vomiting[b]
Davis 5120	23/F	4 (1)	[10 hrs]	Digestive	Nausea, vomiting, and diarrhea[b]
Ferraro 5013	25/F	2	3 (0)	Digestive	Diarrhea[b]
Macek 6084	62/M	3	9 (2)	Digestive	Diarrhea[b]
Maloney 5964	47/M	4 (0)	[5 min]	Digestive	Vomiting[b]
Newcomb 5770	37/M	4 (0)	8 (4)	Body as a whole	Cellulitis
Ong 5019	41/M	6	8 (0)	Digestive	Dyspepsia[b]
Page 5236	38/F	2 (0)	36 (34)	Digestive	Dysphagia
Shah 5994	27/F	4 (0)	7 (3)	Nervous	Nervousness
		4 (0)	7 (3)	Body as a whole	Asthenia
Widman 5417	24/M	3	Cont.: 377 (373)	Metabolic and nutritional	SGOT increased[b]

Note: Study drug was prematurely discontinued for 1 additional patient in the CDTR-PI 200 mg group in whom adverse event was listed as a secondary reason for discontinuation (listed in Appendix 16.2.7.4). Bettis 5428 was classified as discontinuing primarily due to therapeutic failure.

[a] Days posttreatment are presented in parentheses; if less than 1 day, duration in hours is presented in brackets; Cont. = event continued as of specified day.

[b] Drug-relationship classified as possible, probable, or definite.

Table 48. Patients Who Prematurely Discontinued Treatment Due to Adverse Events (cont.)

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution	Body System	COSTART Term
Patients Discontinued from the Cefadroxil Monohydrate 500 mg BID Treatment Group					
Bettis 5078	35/M	1	8 (5)	Body as a whole	Asthenia[b]
		2	3 (0)	Digestive	Diarrhea[b]
		3 (0)	4 (1)	Digestive	Diarrhea[b]
Brandon 5045	75/F	3	[3 hr]	Body as a whole	Abdominal pain
Bruya 5413	22/F	1	4 (1)	Body as a whole	Abdominal pain[b]
		1	4 (1)	Digestive	Diarrhea[b]
		1	4 (1)	Nervous	Dizziness[b]
Ferraro 5392	35/M	3	5 (1)	Digestive	Diarrhea[b]
Kaplan 5780	60/F	1 (0)	3 (2)	Digestive	Nausea[b]
Macek 5173	32/F	4	5 (0)	Digestive	Nausea[b]
Post 5483	19/F	5	13 (7)	Urogenital	Salpingitis
Ruoff 5380	76/F	1 (0)	[3 hrs]	Digestive	Dyspepsia[b]
		2 (1)	[5 hrs]	Digestive	Diarrhea[b]
		2 (1)	[5 hrs]	Nervous	Dizziness[b]
		2 (1)	[5 hrs]	Digestive	Nausea[b]
Suchyta 5323	15/M	1 (0)	3 (2)	Body as a whole	Headache[b]
		1 (0)	2 (1)	Nervous	Nervousness[b]
		2 (1)	3 (2)	Digestive	Nausea[b]
		2 (1)	[5 hrs]	Digestive	Vomiting[b]
Teguh 5883	41/F	1	5 (0)	Body as a whole	Headache[b]

Note: Study drug was prematurely discontinued for 1 additional patient in the CDTR-PI 200 mg group in whom adverse event was listed as a secondary reason for discontinuation (listed in Appendix 16.2.7.4). Bettis 5428 was classified as discontinuing primarily due to therapeutic failure.

[a] Days posttreatment are presented in parentheses; if less than 1 day, duration in hours is presented in brackets; Cont. = event continued as of specified day.

[b] Drug-relationship classified as possible, probable, or definite.

Clinical Laboratory Values: The tests and clinical laboratory values used to determine abnormal conditions were identical to those methods or procedures described in study Cef-97-009.

Mean values at baseline and post-therapy, and mean change from baseline to post-therapy in clinical laboratory test variables as determined by the sponsor are presented in Table 49. Statistically significant treatment differences were observed among the treatment groups in mean change from baseline to post-therapy in potassium, alkaline phosphatase, albumin, and calcium. However, the differences among the treatment groups were not considered to be clinically meaningful. Statistically significant differences in mean change from baseline to post-therapy were observed in some pairwise comparisons of the treatment groups, but none were considered to be clinically significant.

Table 49. Statistically Significant Differences Among Treatment Groups in Mean Change From Baseline to Post-Therapy for Laboratory Test Parameters

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CFDX-MN 500 mg BID	
Chemistry Parameter (unit)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Potassium (mEq/dL)						
Baseline	268	4.32 (0.45)	271	4.24 (0.36)	267	4.25 (0.40)
Post-Therapy	247	4.24 (0.41)	237	4.25 (0.36)	244	4.24 (0.41)
Mean Change to Post-Therapy (p=0.017)	239	-0.09 (0.48)[@$]	232	0.01 (0.36)	238	0.00 (0.38)
Alkaline Phosphatase (U/L)						
Baseline	271	75.83 (28.17)	273	81.64 (55.20)	271	77.64 (34.34)
Post-Therapy	252	74.27 (28.68)	241	79.76 (52.51)	244	76.30 (33.13)
Mean Change to Post-Therapy (p=0.025)	246	-1.63 (9.88)[@]	238	-3.86 (10.67)[#]	242	-1.90 (8.76)
Albumin (g/dL)						
Baseline	271	4.12 (0.35)	276	4.16 (0.31)	267	4.14 (0.38)
Post-Therapy	253	4.08 (0.33)	240	4.18 (0.31)	244	4.11 (0.36)
Mean Change to Post-Therapy (p=0.007)	247	-0.06 (0.28)[@]	239	0.01 (0.25)[#]	238	-0.04 (0.23)
Calcium (mg/dL)						
Baseline	274	9.44 (0.39)	277	9.43 (0.38)	271	9.42 (0.39)
Post-Therapy	255	9.35 (0.37)	241	9.43 (0.39)	245	9.37 (0.38)
Mean Change to Post-Therapy (p=0.012)	251	-0.09 (0.42)[@]	241	0.01 (0.38)[#]	243	-0.07 (0.38)

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; SD = standard deviation
[@] = Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg, p≤0.05.
[$] = Statistically significant difference between CDTR-PI 200 mg and CFDX-MN, p≤0.05.
[#] = Statistically significant difference between CDTR-PI 400 mg and CFDX-MN, p≤0.05.

Deaths: There were no deaths reported during the study.

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Combined Results from Studies Cef-97-009 and Cef-97-011.

Clinical Efficacy

The following tables show the combined results from the two clinical studies. The data from the re-analysis tables were selected since these represent all of the clinical data submitted by the applicant. The combined data show the 200 mg cefditoren group to have a higher cure rate than the 400 mg cefditoren group throughout the evaluations conducted by the sponsor. At the final evaluation, the 200 mg cefditoren group had a cure rate of 80% compared to a cure rate of 76% for the 400 mg cefditoren group. The clinical cure rates for both cefditoren groups were lower than the cure rates for the comparator drugs; however, the 200 mg cefditoren group did almost as well as the patients who received the comparator drugs, 80% versus 81%.

Among the microbiologically evaluable patients, the 200 mg cefditoren group and the 400 mg cefditoren group were comparable to each other and the control group. At the final evaluation by the sponsor, the 200 mg cefditoren group had a 75% cure rate compared to a 76% cure rate for the 400 mg cefditoren group and a 77% cure rate for the comparator drug group.

Clinical Reviewer's Note: *The data from studies Cef-97-009 and Cef-97-011 were combined since both trials followed similar protocols, using similar patients, identical cefditoren doses, similar comparator drugs, similar assessment methods, and identical endpoints. There were no major differences between the two studies that would prevent the data from being combined.*

Microbiology

Table 48 shows the combined pathogen eradication data for the two target pathogens, *S. aureus* and *S. pyogenes*. The data were taken from the reanalysis table since it contains a complete listing of the evaluations made by the applicant. Both cefditoren doses were comparable to each other and the control drugs in eradicating *S. aureus*. At the final evaluation, the eradication rate for the 200 mg cefditoren group was 76% compared to 78% for the 400 mg cefditoren group and 79% for the control drugs. The number of isolates of *S. pyogenes* was much smaller for all of the treatment arms, with the control drug group having only eight isolates. The two cefditoren groups had twice as many isolates with comparable eradication rates.

Clinical Reviewer's Note: *Because of the small number of S. pyogenes isolates in the control drug group, no conclusions can be made with regard to an accurate comparison for the cefditoren groups. Both doses of cefditoren appear to be comparable in eradicating this species, which is known to be highly susceptible to most β-lactam antibiotics.*

Table 50. Re-analysis of Clinical and Patient Microbiological Data

Combined Results from Studies Cef-97-009 and 011.
Evaluable Patients at the Follow-Up Visit

Treatment Group	Initial Submission 12-28-99	Override of Investigator's Clinical Improvements	Override of Investigator's Cures & Clinical Improvements
Cefditoren 200 mg group			
Clinical cures	443/523 (85%)	425/523 (81%)	417/523 (80%)
Patient Micro. Cures	211/255 (83%)	196/255 (77%)	191/255 (75%)
Cefditoren 400 mg group			
Clinical cures	427/516 (83%)	396/516 (77%)	394/516 (76%)
Patient Micro. Cures	222/270 (82%)	207/270 (77%)	206/270 (76%)
Comparator drugs			
Clinical cures	445/513 (87%)	422/513 (82%)	418/513 (81%)
Patient Micro. Cures	193/237 (81%)	184/237 (78%)	182/237 (77%)

Table 51. Re-analysis of the Pathogen Eradication Data
Combined Results from Studies Cef-97-009 and 011.
Evaluable Patients at the Follow-Up Visit

Treatment Group	Initial Submission 12-28-99	Override of Investigator's Clinical Improvements	Override of Investigator's Cures & Clinical Improvements
Cefditoren 200 mg group			
S. aureus	131/158 (83%)	123/158 (78%)	120/158 (76%)
S. pyogenes	19/21 (90%)	16/21 (76%)	16/21 (76%)
Cefditoren 400 mg group			
S. aureus	145/175 (83%)	137/175 (78%)	137/175 (78%)
S. pyogenes	14/15 (93%)	12/15 (80%)	12/15 (80%)
Comparator drugs			
S. aureus	129/153 (84%)	123/153 (80%)	121/153 (79%)
S. pyogenes	8/8 (100%)	7/8 (88%)	7/8 (88%)

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Safety

The following tables were taken from the applicant's integrated summary of safety; each shows a summary of the combined results of the adverse event data for both studies.

Table 52. Summary of Overall Adverse Events Reported During Treatment in Uncomplicated Skin and Skin Structure Infections.

(Studies Cef-97-009 and Cef-97-011)

Body System Adverse Event	Cefditoren 200 mg (N=569)	Cefditoren 400 mg (N=560)	All-Comparators Combined (N=556)
Overall[a]	221 (39%)	252 (45%)	199 (17%)
Digestive Diarrhea	123 (22%) 82 (14%)	173 (31%) 116 (21%)	93 (36%) 40 (7%)

[a] Number of patients with one or more adverse events.

In the combined skin and skin structure infection studies, 39% of the patients in the 200 mg cefditoren group, 45% of the patients in the 400 mg cefditoren group, and 36% of the patients in the all comparators combined group reported at least one adverse event during treatment. Diarrhea and adverse events associated with the digestive system were reported by greater proportions of the 400 mg cefditoren treated patients compared to the 200 mg cefditoren treated patients and the all comparator treated patients.

Table 53. Summary of Overall Treatment-Related Adverse Events Reported During Treatment in Uncomplicated Skin and Skin Structure Infections.

(Studies Cef-97-009 and Cef-97-011)

Body System Adverse Event	Cefditoren 200 mg (N=569)	Cefditoren 400 mg (N=560)	All-Comparators Combined (N=556)
Overall[a]	152 (27%)	189 (34%)	133 (24%)
Digestive Diarrhea	112 (20%) 81 (14%)	155 (28%) 107 (19%)	85 (15%) 40 (7%)

[a] Number of patients with one or more treatment-related adverse events.

In the combined skin and skin structure infection studies, 27% of the patients in the 200 mg cefditoren group, 34% of the patients in the 400 mg cefditoren group, and 24% of the patients in

the all comparators combined group reported at least one treatment-related adverse event during treatment. Again, diarrhea and digestive disorders occurred more often among the patients who received the 400 mg dose of cefditoren.

Clinical Reviewer's Conclusions Regarding NDA 21-222, Protocols Cef-97-009 and 011.

The applicant is requesting approval of an NDA for Spectracef (cefditoren) with an indication for the treatment of uncomplicated skin and skin structure infections caused by *S. aureus and S. pyogenes*. In support of this request, data from two clinical trials (Cef-97-009 and Cef-97-011), one adult study with 63 investigators and 857 patients, and a second adult study with 69 investigators and 828 patients, were submitted.

Both studies were randomized, double-blinded, comparative, multi-center studies with three parallel treatment groups. In study Cef-97-009, patients who met the selection criteria were randomly assigned in a 1:1:1 ratio to receive either cefditoren pivoxil 200 mg BID for 10 days, cefditoren pivoxil 400 mg BID for 10 days, or cefuroxime axetil 250 mg BID for 10 days. In study Cef-97-011, the comparator group received cefadroxil monohydrate 500 mg BID for 10 days.

In study Cef-97-009, there were 265 clinically evaluable patients with 188 pathogens in the 200 mg cefditoren treatment group, 257 clinically evaluable patients with 203 pathogens in the 400 mg cefditoren treatment group, and 265 clinically evaluable patients with 176 pathogens in the cefuroxime axetil treatment group. The clinical cure rates for these treatment groups were 223/265 (84%), 216/257 (84%), and 234/265 (88%) respectively. The cure rates for the microbiologically evaluable patients were 110/135 (81%), 121/143 (85%), and 103/121 (85%), respectively.

Among the 188 baseline isolates in the 200 mg cefditoren group, 152 (81%) were eradicated, while 172 of the 203 (85%) isolates in the 400 mg cefditoren group were eradicated. In the cefuroxime group, 156 of the 176 isolates were eradicated for an 89% eradication rate at the test of cure visit. The eradication rate for *S. aureus* in the 200 mg cefditoren group was 67/81 (83%) and 76/87 (87%) in the 400 mg cefditoren group, compared to 59/67 (88%) in the comparator group. There was a significant difference between the eradication rates by the 200 mg cefditoren group and the cefuroxime group. For *S. pyogenes*, the eradication rates at the Follow-Up visit were comparable with values of 9/10 (90%), 9/10 (90%), and 6/6 (100%), respectively. The number of *S. pyogenes* isolates was small in all of the treatment arms.

In study Cef-97-011, there were 258 clinically evaluable patients with 151 pathogens in the 200 mg cefditoren treatment group, 259 clinically evaluable patients with 165 pathogens in the 400 mg cefditoren treatment group, and 248 clinically evaluable patients with 158 pathogens in the cefadroxil monohydrate treatment group. The clinical cure rates for these treatment groups were 220/258 (85%), 211/259 (81%), and 211/248 (85%) respectively. The cure rates for the microbiologically evaluable patients were 101/120 (84%), 101/127 (80%), and 90/116 (78%), respectively.

The overall eradication rates in the study showed the 200 mg dose of cefditoren to be the most effective at 87% (132/151), followed by the 400 mg dose at 82% (135/165), and the cefadroxil dose at 77% (121/158). The 200 mg cefditoren dose was the most effective at eradicating *S. aureus* with an 83% rate, followed by cefadroxil at 81% and the 400 mg cefditoren dose at 78%. These data differ from those in the previous study where the higher dose had a higher eradication rate for this pathogen, 87% versus 83%. The number of *S. pyogenes* isolates in all three treatment arms was very small with all drugs showing good eradication rates.

The applicant was requested to submit the case report forms with the treatment group blinded for 90 randomized patients, 30 patients from each arm of the study, for both clinical trials. A total of 180 case report forms were submitted on April 24, 2000. The FDA analysis of these patient groups for each study was then compared to the applicant's results for these groups.

In study Cef-97-009, the clinical cure rates for the three blinded treatment groups were as follows: 23/28 (82.1%) for the 200 mg cefditoren group, 22/26 (84.6) for the 400 mg cefditoren group, and 24/26 (92.3%) for the cefuroxime axetil group. In the FDA analysis, the cure rates for these treatment groups were 23/28 (82.1%), 20/26 (76.9%), and 23/26 (88.5%), respectively. The results of both the applicant and FDA's analysis show the two cefditoren doses to be comparable in efficacy, with a higher cure rate among the 200 mg cefditoren patients.

In study Cef-97-011, the clinical cure rates for the three blinded treatment groups were as follows: 24/27 (88.9%) for the 200 mg cefditoren group, 20/26 (76.9%) for the 400 mg cefditoren group, and 21/28 (75.0%) for the cefadroxil monohydrate group. In the FDA analysis, the cure rates for these treatment groups were 22/27 (81.5%), 19/25 (76.0%), and 20/28 (71.4%), respectively. In both the applicant and FDA's analysis of these patient groups, the patients receiving the 200-mg dose of cefditoren had a higher cure rate than those receiving the 400-mg dose.

During the comparison of the applicant and FDA's analysis, two major issues developed concerning the differences between the results. The first issue involved patients who were evaluated as clinical improvements by the investigators and then, subsequently overridden by the applicant to clinical cures or clinical failures, most often clinical cures. The applicant was asked to re-evaluate these patients as follows: At the follow-up visit, patients with three or more signs/symptoms present were to be listed as clinical failures, while patients with two or fewer signs/symptoms present were to be considered as clinical cures. Also, the applicant was asked to look at the results for the investigator determined clinical cures using the same criteria. The second issue concerned a difference in microbiological outcome for patients who were listed as clinical failures or relapses at the follow-up visit. In the applicant's analysis, there were several patients who were clinical failures or relapses, but considered microbiological cures. In FDA's analysis, these patients were considered as both clinical and microbiological failures. The applicant was requested to change the microbiological results to failures for all patients who were clinical failures or clinical relapses.

The applicant completed the re-evaluation of both the investigator-assigned clinical cures and clinical improvements based on their signs/symptoms at the follow-up visit and submitted the results on August 31, 2000. In study Cef-97-009, the clinical cure rates for the three treatment

groups after completing the re-evaluation were as follows: in the 200 mg cefditoren group 212/265 (80%), in the 400 mg cefditoren group 201/257 (78%), and in the 250 mg cefuroxime group 223/265 (84%). Among the microbiologically evaluable patients, the cure rates were 103/135 (76%), 113/143 (79%), and 98/121 (81%), respectively.

The re-evaluation of the clinical data by the applicant resulted in a reduction in cure rates for both the clinically evaluable patients and the microbiologically evaluable patients across all three treatment arms. The reductions in cure rates were 4% for both the 200 mg cefditoren group and the cefuroxime group, and 6% for the 400 mg cefditoren group. At each evaluation step, the 200 mg cefditoren dose performed better than the 400 mg cefditoren dose, 80% versus 78% at the last analysis. Cefuroxime outperformed both cefditoren doses at 84%. The cure rates for all three groups were comparable according to the lower bounds of the 95% confidence intervals determined by the applicant. For the microbiologically evaluable patients, the reduction in cure rates were 5% for the 200 mg cefditoren group, 6% for the 400 mg cefditoren group, and 4% for the cefuroxime group. The cure rates for the three treatment arms are equivalent according to the 97.5% CIs for the differences as determined by the applicant and the FDA.

The re-evaluation also resulted in reductions in the eradication rates for the two target pathogens. For *S. aureus*, the eradication rate in the 200 mg cefditoren group changed from 83% to 78%, in the 400 mg cefditoren group from 87% to 83%, and in the cefuroxime group from 88% to 82%. For *S. pyogenes*, the eradication rate changed from 90% to 80% in the 200 mg cefditoren group, and from 100% to 83% in the cefuroxime group. There was no change in the rate for the 400 mg cefditoren group.

In study Cef-97-011, the clinical cure rates for the three treatment groups after the re-evaluation were as follows: in the 200 mg cefditoren group 205/258 (79%), in the 400 mg cefditoren group 193/259 (75%), and in the 500 mg cefadroxil group 195/248 (79%). The cure rates for the microbiologically evaluable patients were 88/120 (73%), 93/120 (73%), and 84/116 (72%), respectively.

The re-evaluation of the clinical data by the applicant resulted in a reduction in cure rates for both the clinically evaluable patients and the microbiologically evaluable patients across all three treatment arms. The reductions in cure rates were 6% for all three treatment groups. At each evaluation step, the 200 mg cefditoren dose performed better than the 400 mg cefditoren dose, 79% versus 75% at the last analysis. Cefadroxil also outperformed the higher cefditoren dose 79% to 75%. The cure rates for all three groups were comparable according to the lower bounds of the 95% confidence intervals as determined by the applicant. For the microbiologically evaluable patients, the reduction in cure rates were 11% for the 200 mg cefditoren group, 7% for the 400 mg cefditoren group, and 6% for the cefadroxil group. The cure rates for the three treatment arms are equivalent according to the 97.5% CIs for the differences as determined by the applicant and the FDA.

The re-evaluation also resulted in reductions in the eradication rates for the two target pathogens. For *S. aureus*, the eradication rate in the 200 mg cefditoren group changed from 83% to 74%, in the 400 mg cefditoren group from 78% to 74%, and in the cefadroxil group from 81% to 77%. For *S. pyogenes*, the eradication rate changed from 91% to 73% in the 200 mg cefditoren group,

and from 100% to 60% in the 400 mg cefditoren group. There was no change in the rate for the 500 mg cefadroxil group.

In the safety analysis, patients who received the higher dose of cefditoren did experience more adverse reactions than those who received the lower dose. In the combined studies, 39% of the patients in the 200 mg cefditoren group, 45% of the patients in the 400 mg cefditoren, and 36% of the patients in the comparator groups reported at least one adverse event during treatment. Diarrhea and adverse events associated with the digestive system were reported more frequently than other events.

Among the 569 patients who received the 200-mg dose of cefditoren, there were 221 (39%) patients overall who experienced an adverse event, with 123 (22%) patients reporting a digestive event including 82 (14%) patients reporting diarrhea. Among the 560 who received 400 mg of cefditoren, there were 252 (45%) patients overall who developed an adverse event, with 173 (31%) reporting an event associated with the digestive system including 116 (21%) reporting diarrhea. There were 556 patients who received either cefuroxime or cefadroxil. Among these patients, there were 199 (36%) overall who developed an adverse event, with 93 (17%) patients reporting an event related to the digestive system including 40 (7%) patients reporting diarrhea. It can be concluded that the 400-mg dose of cefditoren causes more adverse events associated with the digestive system than either the 200-mg dose or the comparator drugs.

Discussion: The Division of Anti-Infective Drug Products has traditionally divided skin and skin structure infections (SSSI) into two broad categories: uncomplicated SSSI and complicated SSSI (Points to Consider Document, Skin and Skin Structure Infection Guidelines presented at the Anti-Infective Advisory Committee Meeting, March 5-7, 1997, and the FDA draft guidance for industry document published on July 21, 1998). The uncomplicated category consists of superficial skin infections, e.g., impetigo, simple abscesses, while the complicated category refers to infections involving deeper soft tissue or ones that require surgical intervention.

The pathogens responsible for the various types of SSSI in both categories also differ. For uncomplicated SSSI, the two most commonly seen pathogens are *S. aureus* and *S. pyogenes*. Traditionally, those two organisms are the only ones included as pathogens for this indication. Other organisms are not universally accepted in the literature as pathogens in this indication; most are considered as colonizers or contaminants. The FDA guidance document states that other organisms may be added; however, the sponsor must provide a scientific rationale as to why they see the organism as being a true pathogen in their studies. In this application, the sponsor has not requested the addition of other skin pathogens to the labeling.

Labeling: The applicant has submitted sufficient data to show that cefditoren is safe and effective in the treatment of uncomplicated skin and skin structure infections in an adult population. Data from two clinical trials show the drug to be effective in the eradication of various types of skin and skin structure infections caused by *S. aureus* and *S. pyogenes*, when used as directed. The applicant has proposed the following statement for the INDICATIONS AND USAGE section: "Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*". Data from the clinical studies show cefditoren to be effective against beta-lactamase producing strains of *S. aureus*, which comprise a vast majority of the isolates. See Microbiology Review of NDA 21-222 for details. Therefore,

the proposed indication should be revised to read as follows: "Uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β-lactamase producing strains) or *Streptococcus pyogenes*".

In the Pediatric Use subsection under PRECAUTIONS, the following statement, based on the age of the participants, should be added: "Safety and effectiveness in children below the age of 12 years have not been established."

With regard to the ADVERSE REACTIONS section of the labeling, diarrhea, nausea, and headache should be listed as adverse events related to cefditoren therapy.

The proposed dosage should be: 200 mg BID for 10 days.

APPEARS THIS WAY
ON ORIGINAL

Recommendation: It is recommended that cefditoren tablets be approved for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β-lactamase producing strains) or *Streptococcus pyogenes*. Additional statements to the labeling should be added as described under Labeling.

James Blank, Ph.D.

David Ross, M.D., Ph.D.

cc: Orig. NDA
HFD-340 HFD-520/ActDivDir/ JSoreth
HFD-520 HFD-520/MTL/DRoss
HFD-520/MO/Ross
ClinRev/Blank
Pharm/Seethaler
Chem/Shetty
Micro/Unowsky
PM/Duvall-Miller

Concurrence only: