frequently occurring treatment-related adverse events were diarrhea (9 %) and abdominal pain (3 %) in the CDTR-PI group, and diarrhea (4 %) and nausea (3 %) in the PCN-VK group. The difference in the incidence of treatment-related diarrhea was statistically significant ($p = 0.017$).

Most treatment-related adverse events in both treatment groups were mild or moderate in intensity. Eight severe treatment-related adverse events were reported in the CDTR-PI group (abdominal pain, headache, and gastrointestinal disorder by 2 patients each, and diarrhea and dyspepsia by 1 patient each); five severe treatment-related events were reported in the PCN-VK group (back pain, diarrhea, vomiting, edema, and urticaria). A summary of treatment-related adverse events, reported by $\geq$3% of patients in either treatment group, is presented by treatment group in Table 17.

Table 17 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=256)					PCN-VK (N=247)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				51	20%				56	23%
BODY AS A WHOLE				13	5%				14	6%
Abdominal pain	4	1	2	7	3%	2	0	0	2	1%
DIGESTIVE SYSTEM				37	14%				26	11%
Diarrhea*	14	8	1	23	9%	5	3	1	9	4%
Nausea	3	2	0	5	2%	6	1	0	7	3%

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; Mod = moderate; Sev = severe

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[a] Treatment-related adverse events occurring in ≥3% of patients in either 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.

Treatment-Related Adverse Events During Post-treatment

During the post-treatment period, 9 (4%) patients in the CDTR-PI group and 5 (2%) patients in the PCN-VK group reported at least one treatment-related adverse event. In the CDTR-PI group, 3 patients reported headache, 2 patients each reported abnormal liver function tests and vaginal moniliasis (female patients); in the PCN-VK group 2 patients reported pharyngitis. All other treatment-related adverse events during the post-treatment period had an incidence <1%. Two patients in the CDTR-PI group reported treatment-related headache of moderate intensity; all other treatment-related adverse events in both treatment groups were mild in intensity.

ANALYSIS OF ADVERSE EVENTS

All Adverse Events

The most common adverse events in the CDTR-PI and PCN-VK groups were associated with the digestive system (16% and 12%, respectively) and the body as a whole (13% and 14%, respectively). A statistically significant difference was observed

between the treatment groups in the incidence of adverse events associated with the skin and appendages body system, with 2% of the CDTR-PI group and 6% of the PCN-VK group reporting these adverse events (p=0.045). A summary of all adverse events grouped by body system is presented in Table 18.

Table 18 Summary of All Adverse Events Grouped by Body System (During Treatment)

Body System	Number (%) of Patients[a]			
	CDTR-PI (N=256)		PCN-VK (N=247)	
OVERALL[b]	91	(36%)	89	(36%)
Body as a Whole	32	(13%)	34	(14%)
Cardiovascular	2	(1%)	2	(1%)
Digestive	42	(16%)	30	(12%)
Hemic and Lymphatic	1	(<1%)	0	(0%)
Metabolic and Nutritional Disorders	0	(0%)	2	(1%)
Musculoskeletal	1	(<1%)	1	(<1%)
Nervous	6	(2%)	5	(2%)
Respiratory	15	(6%)	23	(9%)
Skin and Appendages*	6	(2%)	15	(6%)
Special Senses	6	(2%)	4	(2%)
Urogenital	1	(<1%)	3	(1%)
Urogenital[c] (females)	2	(1%)	3	(2%)

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[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.

During the post-treatment period, among patients in the CDTR-PI and PCN-VK groups, adverse events associated with the body as a whole were reported by 8 % and 11% of patients, respectively, and adverse events associated with the respiratory system were reported by 7 % and 5 % of patients, respectively. All other body system adverse events had an incidence ≤ 3% during the post-treatment period.

Treatment-Related Adverse Events

The most common treatment-related adverse events in the CDTR-PI and PCN-VK groups were associated with the digestive system (14 % and 11 %, respectively) and the body as a whole (5 % and 6 %, respectively). A statistically significant difference was observed between the treatment groups in the incidence of adverse events associated with the respiratory system, with none of the CDTR-PI group and 3 % of the PCN-VK group reporting these adverse events (p = 0.007). A summary of treatment-related adverse events grouped by body system is presented in Table 19.

Table 19 Summary of Treatment-Related Adverse Events Grouped by Body System (During Treatment)

Body System	Number (%) of Patients[a]			
	CDTR-PI (N=256)		PCN-VK (N=247)	
OVERALL[b]	51	(20%)	56	(23%)
Body as a Whole	13	(5%)	14	(6%)
Digestive	37	(14%)	26	(11%)
Metabolic and Nutritional Disorders	0	(0%)	2	(1%)
Musculoskeletal	0	(0%)	1	(<1%)
Nervous	4	(2%)	3	(1%)
Respiratory**	0	(0%)	7	(3%)
Skin and Appendages	4	(2%)	9	(4%)
Special Senses	0	(0%)	1	(<1%)
Urogenital	0	(0%)	2	(1%)
Urogenital[c] (females)	2	(1%)	3	(2%)

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

** Indicates statistical significance at the 0.01 level, using Fisher's exact test to compare treatment groups.

[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.

Adverse Events by Patient Groups

There were no statistically significant treatment differences in the incidence of adverse events during treatment in patient groups categorized by gender, age, and race. The incidence of treatment-related adverse events in these patient groups was also similar in the two treatment groups.

MEDICAL OFFICER'S COMMENTS:

A statistically significant treatment difference was observed in the incidence of treatment-related diarrhea, with 9% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p=0.017).

STUDY NUMBER CEF 97-010

Evaluation of a random sample of 60 case report forms showed no significant discrepancies, hence sponsor's data are used for this review without re-adjudication by the medical officer. Comments by the medical officer are provided in the sections titled Medical Officer's Comments

STUDY INVESTIGATORS

List of study investigators and the number of enrolled patients is presented in Table 20.

Table 20 Distribution of All Enrolled Patients by Investigator

Investigator	Site	Treatment Group	
		CDTR-PI 200 mg BID	PCN-VK 250 mg QID
Andrews	Atlanta, GA	1	2
Baird	Fargo, ND	2	3
Bettis	Edmonds, WA	17	17
Bock	Harleysville, PA	4	4
Cannon	Winston-Salem, NC	2	1
Christensen	Salt Lake City, UT	9	9
Collins	Champaign, IL	2	2
DeAbate	Harvey, LA	1	2
Dewan	Omaha, NE	1	2
Drehobl	San Diego, CA	4	4
Durden	Tallassee, AL	8	9
Faircloth	Birmingham, AL	3	2
Feicht	Zanesville, OH	1	0
Franck	Portland, OR	1	0
George	Bardstown, KY	2	2
Gooch, III	Salt Lake City, UT	19	20
Hedrick	Bardstown, KY	8	8
Henry	Salt Lake City, UT	19	20
Interiano	Houston, TX	0	1
Jefferson	Little Rock, AR	2	2
Jorgenson	Salt Lake City, UT	3	2
Keating	Scotland, PA	7	7
Konzen	Granite City, IL	2	0
MacPherson	Salt Lake City, UT	8	9
Mazzone	San Luis Obispo, CA	4	4
McAdoo	Milan, TN	2	2
McCulloch	Eclectic, AL	2	1
Morris	Tulsa, OK	2	1
Nett	San Antonio, TX	1	0
Newcomb	Tuscaloosa, AL	2	1
Oandasan	Lake Jackson, TX	1	2
Orchard	Boise, ID	14	15
Page	Tempe, AZ	3	4
Puopolo	Milford, MA	2	3
Reisinger	Pittsburgh, PA	5	6
Rhudy	Salt Lake City, UT	18	19
Richards	Salt Lake City, UT	10	10
Riff	Anaheim, CA	2	2
Riffer	Phoenix, AZ	4	5
Rosenthal	Houston, TX	2	0
Spitzer	Kalamazoo, MI	6	7
Stringer	Manlius, NY	1	0
Suchyta	Salt Lake City, UT	36	34
Wang	Covina, CA	1	1
White, Sr.	Lexington, TN	4	3
Williams, II	Trenton, TN	3	3
Wingert	Fresno, CA	3	3
	TOTAL	**254**	**254**

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

DISPOSITION OF PATIENTS BY DATA SET

Of the 508 randomized patients, 368 (183 in the CDTR-PI group and 185 in the PCN-VK group) were clinically evaluable and 140 (71 in the CDTR-PI group and 69 in the PCN-VK group) were excluded from the per protocol clinical efficacy analyses at the post-therapy visit.

Of the 140 patients who were not evaluable, 106 (53 in each treatment group) did not have a pretreatment culture positive for *S. pyogenes*, 11 patients did not have a clinical response assessed within the specified visit window, 9 patients received less than 3 consecutive days of study drug, 8 patients received less than 80% of the prescribed study drug, 3 patients were lost to follow-up, 2 patients received additional antimicrobials, and 1 patient broke the treatment blind prior to the Post-Therapy Visit.

At the follow-up visit, 360 patients (180 in each treatment group) were clinically evaluable and 148 (74 in each treatment group) were excluded from the clinically evaluable efficacy analyses.

Of the 508 randomized patients, 364 (181 in the CDTR-PI group and 183 in the PCN-VK group) patients were microbiologically evaluable and 144 (73 in the CDTR-PI group and 71 in the PCN-VK group) were excluded from the evaluable microbiologic efficacy analyses at the Post-Therapy Visit. Reasons patients were not microbiologically evaluable were the same as for clinical evaluability. Four additional patients did not have a culture obtained within the visit window.

At the Follow-Up Visit, 355 (179 in the CDTR-PI group and 176 in the PCN-VK group) patients were microbiologically evaluable and 153 (75 in the CDTR-PI group and 78 in the PCN-VK group) were excluded from the microbiologically evaluable efficacy analyses. Disposition of patients by data set is presented in Table 21.

Table 21 Disposition of Patients by Data Set		
	CDTR-PI	**PCN-VK**
All Patients: Total Randomized and Received Study Drug	254	254
S. pyogenes not isolated pretreatment	53	53
Intent-to-Treat Analyses	201	201
Included in the per protocol Efficacy Analyses:		
Post-Therapy	183	185
Follow-Up	180	180
Excluded at Post-Therapy:	71	69
No target pathogen isolated pretreatment	53	53
No clinical response assessment within visit window	4	7
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Received additional antimicrobials	1	1
Treatment blind broken prior to visit	1	0
Excluded at Follow-Up:	74	74
No target pathogen isolated pretreatment	53	53
No clinical response assessment within visit window	5	8
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Received additional antimicrobials	3	5
Lost to follow-up	3	0
Treatment blind broken prior to visit	1	0
Included in the Microbiologically Evaluable Efficacy Analyses:		
Post-Therapy	181	183
Follow-Up	179	176
Excluded at Post-Therapy:	73	71
No target pathogen isolated pretreatment	53	53
No culture obtained within visit window	6	9
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Received additional antimicrobials	1	1
Treatment blind broken prior to visit	1	0
Excluded at Follow-Up:	75	78
No target pathogen isolated pretreatment	53	53
No culture obtained within visit window	6	12
Received less than 3 consecutive days of study drug	6	3
Received additional antimicrobials	3	5
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Treatment blind broken prior to visit	1	0

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

DEMOGRAPHICS

The two treatment groups were comparable regarding the variables of age, sex, race, height and weight. Sixty-five percent (65%) of the patients were females and 87% were Caucasian. Mean age of the study population was 26.8 years and age ranged from 11 to 74 years. Table 22 summarizes demographic data on all the enrolled patients.

Table 22 Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group CDTR-PI		PCN-VK		P-value[a]
Total Treated	254		254		
Gender					0.228
Female	157	(62%)	171	(67%)	
Male	97	(38%)	83	(33%)	
Race					0.742[b]
Caucasian	219	(86%)	225	(89%)	
Hispanic	20	(8%)	17	(7%)	
Black	10	(4%)	10	(4%)	
Asian	1	(<1%)	1	(<1%)	
Other	4	(2%)	1	(<1%)	
Age (years)[c]					0.475
<18	72	(28%)	56	(22%)	
18 – 30	93	(37%)	99	(39%)	
31 – 45	77	(30%)	81	(32%)	
>45	12	(5%)	18	(7%)	
Mean (SD)	26.4 (10.9)		27.1 (11.0)		
Range	11 - 74		12 – 72		
Weight (pounds)[c]					0.053
<135	82	(32%)	74	(29%)	
135 – 165	85	(33%)	66	(26%)	
166 – 195	43	(17%)	58	(23%)	
>195	44	(17%)	56	(22%)	
Mean (SD)	156.9 (41.6)		164.3 (43.9)		
Range	75 - 311		83 – 342		
Height (inches)[c]					0.650
Mean (SD)	66.0 (4.0)		66.2 (3.9)		
Range	55 - 78		54 – 76		

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

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Among per protocol patients a statistically significant difference between the two groups was seen in weight at baseline. Patients were heavier on average in the penicillin group than in the cefditoren group (mean weights 162.2 and 152.2 respectively, p value 0.018). Table 23 summarizes demographic data on per protocol patients.

Table 23 Demographic Information (Per protocol Patients)

Demographic Characteristic	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	183		185		
Gender					0.912
Female	121	(66%)	124	(67%)	
Male	62	(34%)	61	(33%)	
Race[b]					0.697
Caucasian	163	(89%)	171	(92%)	
Black	4	(2%)	3	(2%)	
Hispanic	12	(7%)	10	(5%)	
Asian	1	(1%)	0	(0%)	
Other	3	(2%)	1	(1%)	
Age (years)[c]					0.345
<18	55	(30%)	41	(22%)	
18 – 30	68	(37%)	73	(39%)	
31 – 45	55	(30%)	63	(34%)	
>45	5	(3%)	8	(4%)	
Mean (SD)	25.6 (10.2)		26.6 (10.2)		
Range	12 - 64		12 – 58		
Weight (pounds)[c]					0.018
<135	65	(36%)	58	(31%)	
135 – 165	63	(34%)	48	(26%)	
166 – 195	29	(16%)	38	(21%)	
>195	26	(14%)	41	(22%)	
Mean (SD)	152.2 (37.8)		162.2 (42.9)		
Range	75 - 311		83 – 323		
Height (inches)[c]					0.179
Mean (SD)	65.8 (3.9)		66.4 (3.7)		
Range	55 - 75		54 – 76		

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

MEDICAL OFFICERS COMMENTS:

The two treatment groups were comparable with respect to age, sex, race, height and weight. Among per protocol patients, the statistically significant difference in weight between the two treatment groups is unlikely to have an impact on the safety and efficacy of the two drugs.

DIAGNOSES AND BASELINE CHARACTERISTICS

Baseline characteristics of the two treatment groups were similar for all patients and for the per protocol patients. The majority (73%) of patients had a diagnosis of

pharyngitis and tonsillitis. The infection was considered moderate (74%) in most patients. Clinical condition was considered to be good (57%) or fair (42%) in most patients. 75% of the patients reported that this was their first streptococcal pharyngitis and/or tonsillitis infection within the past year while 24% reported two to four infections (including the current infection) within the past year. The following two tables summarize diagnoses and baseline characteristics in all and per protocol patients respectively:

Table 24 Summary of Diagnoses and Baseline Characteristics (All Patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	254		254		
Diagnosis					0.756
Pharyngitis and tonsillitis	183	(72%)	189	(74%)	
Pharyngitis	59	(23%)	52	(20%)	
Tonsillitis	12	(5%)	13	(5%)	
Number of Infections Within Past Year[b]					0.441
1	185	(73%)	197	(78%)	
2 – 4	67	(26%)	56	(22%)	
>4	2	(1%)	1	(<1%)	
Infection Status					0.099
Mild	44	(17%)	29	(11%)	
Moderate	182	(72%)	193	(76%)	
Severe	28	(11%)	32	(13%)	
Clinical Condition					0.168
Good	153	(60%)	137	(54%)	
Fair	98	(39%)	114	(45%)	
Poor	3	(1%)	3	(1%)	
Smoking Status					0.580
Non-smoker	187	(74%)	193	(76%)	
Smoker	40	(16%)	41	(16%)	
Ex-smoker	27	(11%)	20	(8%)	
Alcohol Use					0.166
Non-drinker	168	(66%)	173	(68%)	
Drinker	76	(30%)	78	(31%)	
Ex-drinker	10	(4%)	3	(1%)	

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values are from Fisher's exact test for diagnosis, number of infections within the past year, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

[b] Number of streptococcal pharyngitis/tonsillitis infections in past 12 months, including current infection.

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Table 25 Summary of Diagnoses and Baseline Characteristics (Per protocol Patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	183		185		
Diagnosis					0.760
Pharyngitis and tonsillitis	136	(74%)	143	(77%)	
Pharyngitis	38	(21%)	35	(19%)	
Tonsillitis	9	(5%)	7	(4%)	
Number of Infections Within Past Year[b]					0.109
1	133	(73%)	148	(80%)	
2 – 4	48	(26%)	37	(20%)	
>4	2	(1%)	0	(0%)	
Infection Status					0.174
Mild	29	(16%)	16	(9%)	
Moderate	131	(72%)	146	(79%)	
Severe	23	(13%)	23	(12%)	
Clinical Condition					0.058
Good	109	(60%)	91	(49%)	
Fair	71	(39%)	91	(49%)	
Poor	3	(2%)	3	(2%)	
Smoking Status					0.401
Non-smoker	137	(75%)	146	(79%)	
Smoker	27	(15%)	27	(15%)	
Ex-smoker	19	(10%)	12	(6%)	
Alcohol Use					0.315
Non-drinker	125	(68%)	128	(69%)	
Drinker	50	(27%)	54	(29%)	
Ex-drinker	8	(4%)	3	(2%)	

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values are from Fisher's exact test for diagnosis, number of infections within the past year, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

[b] Number of streptococcal pharyngitis/tonsillitis infections in past 12 months, including current infection.

MEDICAL OFFICER'S COMMENTS:

Both all and per protocol patients were comparable with regard to diagnosis of pharyngitis and/or tonsillitis, number of infections within the past year, infection status, clinical condition, smoking status and alcohol use in the two treatment groups.

PRE-TREATMENT SIGNS AND SYMPTOMS

Pre-treatment signs and symptoms in all patients and per protocol patients were similar in the two treatment groups. Besides sore throat, the most frequently reported signs/symptoms were pharyngeal erythema and tonsillar erythema. Summary of pre-treatment signs and symptoms for all and per protocol patients is presented in the following two tables respectively:

Table 26 Summary of Pretreatment Signs and Symptoms (All Patients)

Sign/Symptom	Number of Patients by Treatment Group		P-value[a]
	CDTR-PI	PCN-VK	
Total Treated	254	254	
Sore Throat	(N=254)	(N=254)	0.204
Mild	36 (14%)	27 (11%)	
Moderate	126 (50%)	125 (49%)	
Severe	92 (36%)	102 (40%)	
Fever	(N=254)	(N=254)	0.633
Absent	234 (92%)	231 (91%)	
Present	20 (8%)	23 (9%)	
Pharyngeal Erythema	(N=254)	(N=254)	0.437
Absent	16 (6%)	12 (5%)	
Present	238 (94%)	242 (95%)	
Pharyngeal Exudate	(N=254)	(N=254)	0.101
Absent	165 (65%)	147 (58%)	
Present	89 (35%)	107 (42%)	
Tonsillar Erythema	(N=220)	(N=225)	0.920
Absent	18 (8%)	19 (8%)	
Present	202 (92%)	206 (92%)	
Tonsillar Exudate	(N=220)	(N=225)	0.619
Absent	100 (45%)	97 (43%)	
Present	120 (55%)	128 (57%)	
Cervical Lymph Node Tenderness	(N=254)	(N=254)	0.254
Absent	52 (20%)	42 (17%)	
Present	202 (80%)	212 (83%)	
Headache	(N=254)	(N=254)	0.926
Absent	90 (35%)	89 (35%)	
Present	164 (65%)	165 (65%)	
Abdominal Pain	(N=254)	(N=254)	0.576
Absent	207 (81%)	202 (80%)	
Present	47 (19%)	52 (20%)	

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.

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Table 27 Summary of Pretreatment Signs and Symptoms (Per protocol Patients)

Sign/Symptom	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	183		185		
Sore Throat	(N=183)		(N=185)		0.455
Mild	24	(13%)	17	(9%)	
Moderate	86	(47%)	92	(50%)	
Severe	73	(40%)	76	(41%)	
Fever	(N=183)		(N=185)		0.365
Absent	234	(92%)	231	(91%)	
Present	20	(8%)	23	(9%)	
Pharyngeal Erythema	(N=183)		(N=185)		0.141
Absent	12	(7%)	6	(3%)	
Present	171	(93%)	179	(97%)	
Pharyngeal Exudate	(N=183)		(N=185)		0.197
Absent	114	(62%)	103	(56%)	
Present	69	(38%)	82	(44%)	
Tonsillar Erythema	(N=161)		(N=167)		0.491
Absent	12	(7%)	16	(10%)	
Present	149	(93%)	151	(90%)	
Tonsillar Exudate	(N=161)		(N=167)		0.869
Absent	67	(42%)	68	(41%)	
Present	94	(58%)	99	(59%)	
Cervical Lymph Node Tenderness	(N=183)		(N=185)		0.202
Absent	37	(20%)	28	(15%)	
Present	146	(80%)	157	(85%)	
Headache	(N=183)		(N=185)		0.338
Absent	65	(36%)	57	(31%)	
Present	118	(64%)	128	(69%)	
Abdominal Pain	(N=183)		(N=185)		0.722
Absent	151	(83%)	150	(81%)	
Present	32	(17%)	35	(19%)	

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.

MEDICAL OFFICER'S COMMENTS:

Pre-treatment signs and symptoms in both all and per protocol patients were similar in the two treatment groups.

MEASUREMENT OF TREATMENT COMPLIANCE

Treatment duration and study drug compliance of per protocol patients were similar in the two treatment groups. Nine patients (6 in the CDTR-PI group and 3 in the PCN-VK group) were clinically and microbiologically not per protocol as they had received less than 3 consecutive days of the study drug. In addition, 8 patients (3 in the CDTR-PI group and 5 in the PCN-VK group) were not evaluable as they took less than 80% of the prescribed drug. Duration of treatment and compliance for per protocol patients are presented in Table 28.

Table 28 Duration of Treatment and Study Drug Compliance (Per protocol Patients)

Total Treated	CDTR-PI 183		PCN-VK 185		P-value[a]
Treatment Duration (days)					0.439
<4	1	(1%)	2	(1%)	
4-7	2	(1%)	3	(2%)	
8-10	61	(33%)	66	(36%)	
>10	119	(65%)	114	(62%)	
Mean (SD)	10.6	(1.1)	10.5	(1.2)	
Min – Max					
Compliance (percentage)[b]					0.821
< 80	3	(2%)	5	(3%)	
80 – 90	10	(5%)	9	(5%)	
>90	170	(93%)	171	(92%)	
Mean (SD)	97.2	(9.4)	97.0	(10.9)	
Min – Max					

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation
[a] P-value for comparison between treatment groups using an F-test.
[b] For patients who did not return study drug containers, compliance was calculated using the number of days on treatment.

MEDICAL OFFICER'S COMMENTS:

Treatment duration and study drug compliance of per protocol patients were similar in the two treatment groups.

PRIMARY EFFICACY RESULTS

(Excerpted from the sponsor's data)

Clinical Response at Post Therapy Visit

PER PROTOCOL PATIENTS

Clinical cure rates at the Post-Therapy Visit were similar in the CDTR-PI (93%) and PCN-VK (89%) treatment groups.

Clinical cure and failure rates at the Post-Therapy Visit for per protocol patients and the confidence interval around the difference in cure rates are presented in the following table.

Clinical Response at the Post-Therapy Visit (Per protocol Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	171/183	(93%)	164/185	(89%)	0.144
Failure	12/183	(7%)	21/185	(11%)	[-1.0, 10.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI around the difference in cure rates was calculated using normal approximation for the binomial distribution.

Clinical cure rates at the Post-Therapy Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections within the past year.

After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test, statistically significant differences were observed for smoking status (p=0.018), clinical condition (p = 0.001), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year (p = 0.013), with higher cure rates for non-smokers, patients in good clinical condition and patients with two to four streptococcal pharyngitis and/or tonsillitis infections within the past year who were treated with CDTR-PI.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT (ITT)

Results in intent-to-treat patients were similar to those in per protocol patients. Clinical cure rates at the Post-Therapy Visit were 89% in the CDTR-PI group and 86% in the PCN-VK group.

Clinical cure and failure rates at the Post-Therapy Visit for ITT patients and the confidence interval around the difference in cure rates are presented in the following table:

Clinical Response at the Post-Therapy Visit (ITT patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	178/201	(89%)	173/201	(86%)	0.549
Failure	23/201	(11%)	28/201	(14%)	[-4.0, 9.0]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in cure rates was calculated using normal approximation for the binomial distribution.

After adjusting for concomitant factors (age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal infections within the past year), no statistically significant differences were observed between treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor was tested, statistically significant differences were observed for alcohol use (p = 0.028) and number of streptococcal pharyngitis and/or tonsillitis infections within the past year (p = 0.049).

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

At the Post-Therapy Visit, a total of 36 patients, 16 in the CDTR-PI group and 20 in the PCN-VK group, were classified by the investigator as clinical improvement. When

the clinical responses for these patients were reassessed at TAP Holdings Inc., 13 patients in the CDTR-PI group were reassessed as clinical cures and 3 as clinical failures. In the PCN-VK group, 16 patients were reassessed as clinical cures and 4 as clinical failures.

MEDICAL OFFICER'S COMMENTS:

The number of patients re-classified from clinical improvement to cures or failures at the post therapy visit was similar in the two treatment groups. No discrepancy in re-classification was noted in the 60 case report forms reviewed by the medical officer. Clinical cure rates at the post therapy visit were similar in the two treatment groups, in both per protocol and ITT patients. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Clinical Response at Follow-Up Visit

PER PROTOCOL PATIENTS

Clinical cure rates were similar at the Follow-Up Visit in the CDTR-PI (89%) and PCN-VK (84%) treatment groups.

The clinical response at the Follow-Up Visit for per protocol patients and the confidence interval around the difference in cure rates are presented in the following table.

Clinical Response at the Follow-Up Visit (Per protocol Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	160/180	(89%)	152/180	(84%)	0.278
Failure	20/180	(11%)	28/180	(16%)	[-2.6, 11.5]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in cure rates was calculated using normal approximation for the binomial distribution.

Clinical cure rates at the Follow-Up Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections within the past year. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test, statistically significant differences were observed for smoking status ($p = 0.018$), alcohol use ($p = 0.022$), clinical condition ($p = 0.022$), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year ($p = 0.007$). Some differences were due to the small number of patients in the

subgroups; higher cure rates were observed for non-smokers, non-drinkers, patients in good clinical condition, and patients with two to four streptococcal pharyngitis and/or tonsillitis infections within the past year who were treated with CDTR-PI.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

Results were similar between the two treatment groups in ITT patients. Clinical cure rates at the Follow-Up Visit were 83% in the CDTR-PI group and 80% in the PCN-VK group.

The clinical response at the Follow-Up Visit for ITT patients and the confidence interval around the difference in cure rates are presented in the following table.

Clinical Response at the Follow-Up Visit (ITT Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	166/201	(83%)	160/201	(80%)	0.524
Failure	35/201	(17%)	41/201	(20%)	[-4.7, 10.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in cure rates was calculated using normal approximation for the binomial distribution.

After adjusting for concomitant factors (age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal infections within the past year), no statistically significant differences were observed between treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor was tested, statistically significant differences were observed for age ($p = 0.016$), smoking status ($p = 0.013$), alcohol use ($p = 0.002$), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year ($p = 0.019$).

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

At the Follow-Up Visit, 3 patients in the CDTR-PI group and 2 patients in the PCN-VK group were classified by the investigator as clinical improvement. When the clinical responses for these patients were reassessed at TAP Holdings Inc., all were reassessed as cures.

MEDICAL OFFICERS COMMENTS:

The number of patients re-classified from clinical improvement to cures or failures at the follow-up visit is comparable in the two treatment arms. In the case report forms reviewed, discrepancy in re-classification was noted with regard to one patient at the follow-up visit. One patient classified as cured by the investigator, was classified as a relapse by the medical officer as clinical signs and symptoms had recurred at the follow-up visit.

Clinical cure rates at the follow-up visit were similar in the two treatment groups, in both per protocol and ITT patients. The 95% confidence intervals around the

difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Microbiologic Response-Post-Therapy Visit

PER PROTOCOL PATIENTS

At the Post-Therapy Visit, microbiologic eradication rates were 88% in the CDTR-PI group and 85% in the PCN-VK group.

Microbiologic eradication and persistence rates at the Post-Therapy Visit and the confidence interval around the difference in eradication rates for per protocol patients are presented in the following table.

Microbiologic Response at the Post-Therapy Visit (Per protocol Patients)

Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	160/181	(88%)	155/183	(85%)	0.357
Persistence	21/181	(12%)	28/183	(15%)	[-3.3, 10.7]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in eradication rates was calculated using normal approximation for the binomial distribution.

When eradication rates at the Post-Therapy Visit were compared using Cochran-Mantel-Haenszel methodology adjusting for concomitant factors, including age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections in the past year, no statistically significant differences were observed between treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor were tested using the Breslow-Day test, statistically significant differences were observed between the two treatment groups for smoking status ($p = 0.036$), clinical condition ($p=0.015$), compliance ($p = 0.047$), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year ($p = 0.013$), with higher eradication rates for non-smokers, patients in good clinical condition, and patients with two to four streptococcal pharyngitis and/or tonsillitis infections in the past year who were treated with CDTR-PI.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

Results were similar between the two treatment groups in ITT patients. Microbiologic eradication rates at the Post-Therapy Visit were 84% in both the CDTR-PI group and the PCN-VK group.

Microbiologic eradication and persistence rates at the Post-Therapy Visit and the confidence interval around the difference in eradication rates for ITT patients are presented in the following table.

Microbiologic Response at the Post-Therapy Visit (ITT Patients)					
Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	168/201	(84%)	169/201	(84%)	>0.999
Persistence	33/201	(16%)	32/201	(16%)	[-7.7, 6.7]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in eradication rates was calculated using normal approximation for the binomial distribution.

After adjusting for concomitant factors (age, gender, race, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal infections within the past year), no statistically significant differences were observed between treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor were tested using the Breslow-Day test, statistically significant treatment differences were observed after adjusting for age ($p = 0.048$), alcohol use ($p = 0.043$), clinical condition ($p = 0.045$), compliance ($p = 0.028$), and number of streptococcal pharyngitis and/or tonsillitis infections in the past year ($p = 0.031$).

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

MEDICAL OFFICERS COMMENTS:

Microbiologic eradication rates in the CDTR-PI group were similar to the PCN-VK group among per protocol (88% and 85% respectively) and ITT patients (84% and 84% respectively) at the post therapy visit. The 95% confidence intervals around the difference in eradication rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Microbiologic Response-Follow-up Visit

PER PROTOCOL PATIENTS

At the Follow-Up Visit, microbiologic eradication rates were 84% in the CDTR-PI group and 78% in the PCN-VK group.

Microbiologic eradication and persistence rates at the Follow-Up Visit and the confidence interval around the difference in eradication rates for per protocol patients are presented in the following table.

Microbiologic Response at the Follow-Up Visit (Per protocol Patients)					
Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	151/179	(84%)	138/176	(78%)	0.173
Persistence	28/179	(16%)	38/176	(22%)	[-2.1, 14.0]

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in eradication rates was calculated using normal approximation for the binomial distribution.

When eradication rates at the Follow-Up Visit were compared using Cochran-Mantel-Haenszel methodology adjusting for concomitant factors, including age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections in the past year, no statistically significant differences were observed between the treatment groups.

When the homogeneity of treatment differences across levels of each concomitant factor were tested using the Breslow-Day test, statistically significant differences were observed for smoking status ($p = 0.009$), alcohol use ($p = 0.009$), clinical condition ($p = 0.026$), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year ($p < 0.001$). Higher eradication rates were observed for non-smokers, non-drinkers, patients in good clinical condition, and patients with two to four streptococcal pharyngitis and/or tonsillitis infections within the past year who were treated with CDTR-PI.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

Results in ITT patients were similar to those in per protocol patients. Eradication rates at the Follow-Up Visit were 79% in the CDTR-PI group and 73% in the PCN-VK group.

Microbiologic eradication and persistence rates at the Follow-Up Visit and the confidence interval around the difference in eradication rates for ITT patients are presented in the following table.

Microbiologic Response at the Follow-Up Visit (ITT Patients)					
Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	158/201	(79%)	147/201	(73%)	0.244
Persistence	43/201	(21%)	54/201	(27%)	[-2.9, 13.8]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

[b] The 95% CI around the difference in eradication rates was calculated using normal approximation for the binomial distribution.

No statistically significant differences were observed between the two treatment groups after adjusting for concomitant factors.

When the homogeneity of treatment differences were tested using the Breslow-Day test, statistically significant differences were observed for age ($p = 0.028$), alcohol use ($p = 0.013$), and number of streptococcal pharyngitis and/or tonsillitis infections within the past year ($p = 0.001$).

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

Based on serotyping results, no CDTR-PI patients and 3 PCN-VK patients were re-infected with a new strain of *S. pyogenes* at the Follow-Up Visit.

MEDICAL OFFICER'S COMMENTS:

Microbiologic eradication rates in the CDTR-PI group were similar to the PCN-VK group among per protocol (84% and 78% respectively) and ITT patients (79% and 73% respectively) at the follow-up visit. The 95% confidence intervals around the difference in eradication rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Clinical Response Versus Microbiologic Response at the Post-Therapy Visit

Microbiologic responses were compared with clinical responses in both treatment groups at the post-therapy visit. Differences occurred in 15 patients in the CDTR-PI group and 12 patients in the PCN-VK treatment group. Twelve CDTR-PI patients and 10 PCN-VK patients demonstrated persistence of *S. pyogenes* while the clinical response was cure. Three patients in the CDTR-PI group and 2 patients in the PCN-VK group demonstrated eradication of *S. pyogenes* while clinical response was assessed as failure. Results in ITT patients were similar. Differences occurred in 20 patients in the CDTR-PI group and 18 patients in the PCN-VK group, most of whom demonstrated persistence of *S. pyogenes* while the clinical response was cure.

Clinical Response Versus Microbiologic Response at the Follow-Up Visit

Microbiologic responses were also compared with clinical responses in both treatment groups at the Follow-Up Visit. Differences occurred in 9 patients in the CDTR-PI treatment group and 15 patients in the PCN-VK treatment group. Eight CDTR-PI patients and 13 PCN-VK patients demonstrated persistence of *S. pyogenes* while the clinical response was cure. One CDTR-PI patient and 2 PCN-VK patients demonstrated eradication of *S. pyogenes* while the clinical response was failure. Results in ITT patients were generally similar. Differences occurred in 12 patients in the CDTR-PI group and 21 patients in the PCN-VK group, most of whom demonstrated persistence of *S. pyogenes* while the clinical response was cure.

SECONDARY EFFICACY VARIABLES

Change from Pre-treatment to Post-Therapy in Signs and Symptoms

There were no statistically significant differences between treatment groups in the percentage of per protocol patients showing resolution or improvement in sore throat, or resolution in fever, pharyngeal erythema, pharyngeal exudate, tonsillar erythema, tonsillar exudate, cervical node tenderness, headache, or abdominal pain at the Post-Therapy Visit. A summary of the resolution and resolution/improvement rates for all signs and symptoms at the Post-Therapy Visit is presented in Table 29.

Table 29 Resolution and Resolution/Improvement of Pretreatment Signs and Symptoms Compared to the Post-Therapy Visit (Per protocol Patients)

Sign/Symptom	CDTR-PI		PCN-VK		P-value[a]
Sore Throat					
Resolution	160/179	(89%)	159/184	(86%)	0.424
Resolution/Improvement	170/179	(95%)	173/184	(94%)	0.819
Fever					
Resolution	12/13	(92%)	18/18	(100%)	0.419
Pharyngeal Erythema					
Resolution	147/167	(88%)	148/178	(83%)	0.223
Pharyngeal Exudate					
Resolution	64/66	(97%)	76/82	(93%)	0.299
Tonsillar Erythema					
Resolution	130/146	(89%)	129/150	(86%)	0.484
Tonsillar Exudate					
Resolution	90/92	(98%)	92/98	(94%)	0.281
Cervical Lymph Node Tenderness					
Resolution	134/143	(94%)	142/156	(91%)	0.515
Headache					
Resolution	108/116	(93%)	118/127	(93%)	1.000
Abdominal Pain					
Resolution	27/29	(93%)	34/35	(97%)	0.586

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values for comparison between treatment groups using Fisher's exact test.

Change from Pre-treatment to the Follow-Up Visit in Signs and Symptoms

There were no statistically significant differences between treatment groups in the percentage of per protocol patients showing resolution or improvement in sore throat, or resolution in fever, pharyngeal erythema, pharyngeal exudate, tonsillar erythema, tonsillar exudate, cervical node tenderness, headache, or abdominal pain at the Follow-Up Visit. A summary of the resolution and resolution/improvement rates for all signs and symptoms at the Follow-Up Visit is presented in Table 30.

Table 30 Resolution and Resolution/Improvement of Pretreatment Signs and Symptoms Compared to the Follow-Up Visit (Per protocol Patients)

Sign/Symptom	CDTR-PI		PCN-VK		P-value[a]
Sore Throat					
Resolution	153/180	(85%)	147/180	(82%)	0.480
Resolution/Improvement	161/180	(89%)	154/180	(86%)	0.339
Fever					
Resolution	12/14	(86%)	15/18	(83%)	1.000
Pharyngeal Erythema					
Resolution	143/168	(85%)	143/174	(82%)	0.470
Pharyngeal Exudate					
Resolution	62/67	(93%)	67/79	(85%)	0.197
Tonsillar Erythema					
Resolution	126/147	(86%)	121/144	(84%)	0.745
Tonsillar Exudate					
Resolution	84/93	(90%)	81/96	(84%)	0.276
Cervical Lymph Node Tenderness					
Resolution	127/144	(88%)	129/153	(84%)	0.401
Headache					
Resolution	98/116	(84%)	102/123	(83%)	0.861
Abdominal Pain					
Resolution	25/32	(78%)	25/32	(78%)	1.000

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values for comparison between treatment groups using Fisher's exact test.

EFFICACY CONCLUSIONS (As provided by the sponsor)

Clinical cure rates among per protocol patients in the CDTR-PI and PCN-VK groups were similar at the Post-Therapy Visit (93% and 89%, respectively) and the Follow-Up Visit (89% and 84%, respectively). Clinical signs and symptoms of streptococcal pharyngitis and/or tonsillitis resolved in the majority of patients treated with either regimen, with no statistically significant differences between the treatment groups at either visit.

Microbiologic eradication rates among per protocol patients in the CDTR-PI and PCN-VK groups were also similar at the Post-Therapy Visit (88% and 85%, respectively) and the Follow-Up Visit (84% and 78%). The 95% CI around the difference in clinical cure rates and the difference in microbiologic eradication rates demonstrated that the two treatment regimens were equivalent.

Results of this study indicate that Cefditoren pivoxil (200 mg BID for 10 days) was as effective as Penicillin VK (250 mg QID for 10 days) in eradicating *S. pyogenes* and in resolving the clinical signs and symptoms of streptococcal pharyngitis and/or tonsillitis.

MEDICAL OFFICERS COMMENTS:

Clinical and microbiologic cure rates at the post therapy and follow-up visits were similar in the per protocol and ITT patients in both treatment groups.

Clinical cure rates in the per protocol patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (93% and 89% respectively) and at the follow-up visit (89% and 84% respectively). The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. Clinical cure rates in the ITT patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (89% and 86% respectively) and at the follow-up visit (83% and 80% respectively). The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent.

Microbiologic cure rates in the per protocol patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (88% and 85% respectively) and at the follow-up visit (84% and 78% respectively). The 95% confidence intervals around the difference in cure rates in the per protocol patients demonstrated that the two treatment regimens were equivalent. Microbiologic cure rates in the ITT patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (84% and 84% respectively) and at the follow-up visit (79% and 73% respectively). The 95% confidence intervals around the difference in cure rates in the ITT group demonstrated that the two treatment regimens were equivalent.

SAFETY EVALUATION

All patients who received at least one dose of study drug (N = 508) were included in the safety analyses.

- **Extent of Exposure**

Of the 508 patients enrolled in the study, 233/254 (92%) patients assigned to Cefditoren Pivoxil 200 mg BID and 236/254 (93%) patients assigned to Penicillin VK 250 mg QID completed the 10-day treatment regimen. A summary of the extent of exposure is presented in Table 31.

Table 31 Extent of Exposure (All Patients)

	CDTR-PI		PCN-VK	
Total Treated	254		254	
Treatment Duration (Days)				
<4	12	(5%)	6	(2%)
4-7	5	(2%)	8	(3%)
8-10	84	(33%)	86	(34%)
>10	153	(60%)	154	(61%)
Mean (SD)	10.2	(2.1)	10.3	(1.7)
Min - Max				

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation

Brief Summary of Adverse Events

During treatment, the incidences of all adverse events and treatment-related adverse events were 38% and 26%, respectively, in the CDTR-PI group and 37% and 20%, respectively, in the PCN-VK group. The most frequently occurring treatment-related adverse events during treatment in both groups were diarrhea and nausea. A

statistically significant difference was observed in the incidence of treatment-related diarrhea, with 11% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event ($p = 0.005$).

No deaths were reported during the study. One patient in each treatment group had a serious adverse event during the study. A 44-year-old male assigned to the CDTR-PI group, required intervention on Day 1 (during treatment) for treatment of a left peritonsillar abscess that was considered to be unrelated to study drug. A 31-year-old male assigned to the PCN-VK group was hospitalized on Day 26 (15 days after the last dose of study drug) for the treatment of four serious adverse events: pulmonary emboli, large atrial thrombus, renal failure, and a hypercoagulation state. All of these adverse events were considered to be possibly related to study drug. On Day 38 (27 days after the last dose of study drug) the patient returned to the hospital for deep vein thrombosis that required intervention; this adverse event was also considered possibly related to study drug.

Seven patients in the CDTR-PI treatment group and 8 patients in the PCN-VK treatment group were prematurely discontinued from treatment due to the occurrence of at least one adverse event. Adverse events leading to discontinuation were most commonly associated with the body as a whole and digestive body systems in the CDTR-PI group and with the digestive, skin and appendages, and body as a whole body systems in the PCN-VK group.

All Adverse Events During Treatment (from the first day of study drug to 3 days after the last dose of study drug)

Of the 508 randomized patients who received study drug, 96 patients (38%) in the CDTR-PI group and 93 (37%) in the PCN-VK group reported at least one adverse event during treatment. The most commonly reported adverse events during treatment in the CDTR-PI and PCN-VK groups included diarrhea (12% and 4%, respectively), headache (6% and 7%, respectively), and nausea (6% and 6%, respectively). The difference between treatment groups in the incidence of diarrhea was statistically significant ($p = 0.003$). A statistically significant treatment difference was also observed for the incidence of abdominal pain ($p = 0.036$), with 4% of the patients in the CDTR-PI group and 1% of the patients in the PCN-VK group reporting this adverse event.

Most adverse events in both treatment groups were mild or moderate in intensity. Twelve severe events were reported in the CDTR-PI group (abscess and migraine by 2 patients each, and chills, headache, diarrhea, nausea, myalgia, abnormal dreams, anxiety, and increased cough by 1 patient each). Five severe events were reported in the PCN-VK group (accidental injury, diarrhea, nervousness, voice alteration, and kidney calculus by 1 patient each). A summary of all adverse events during treatment reported by $\geq 3\%$ of patients is presented in Table 32.

Table 32 Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=254)					PCN-VK (N=254)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				96	38%				93	37%
BODY AS A WHOLE				32	13%				37	15%
Headache	8	6	1	15	6%	7	11	0	18	7%
Abdominal pain*	6	4	0	10	4%	0	2	0	2	1%
DIGESTIVE SYSTEM				51	20%				31	12%
Diarrhea*	16	13	1	30	12%	7	3	1	11	4%
Nausea	7	7	1	15	6%	11	4	0	15	6%
Vomiting	3	4	0	7	3%	1	4	0	5	2%
NERVOUS SYSTEM				8	3%				16	6%
Dizziness	2	0	0	2	1%	4	3	0	7	3%
RESPIRATORY SYSTEM				10	4%				17	7%
Rhinitis	2	0	0	2	1%	4	4	0	8	3%
Cough increased	2	0	1	3	1%	1	6	0	7	3%
SKIN & APPENDAGES				14	6%				11	4%
Rash	6	1	0	7	3%	2	0	0	2	1%
UROGENITAL SYSTEM (FEMALE)[d]				N=157					N=171	
				5	3%				7	4%
Vaginal moniliasis	2	0	0	2	1%	5	1	0	6	4%

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; Mod = moderate; Sev = severe

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[a] Adverse events occurring in ≥ 3% of patients in either 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] Female-specific adverse events.

All Adverse Events Post-treatment (at least 4 days after the last dose of study drug)

During the post-treatment period, 54 (21%) patients in the CDTR-PI group and 59 (23%) patients in the PCN-VK group reported at least one adverse event. In the CDTR-PI group, headache was reported by 7% of patients and in the PCN-VK group, headache and pharyngitis were each reported by 4% of patients. All other adverse events reported during the post-treatment period had an incidence ≤ 2%. Three severe events (abdominal pain, back pain, and tooth disorder by 1 patient each) were reported in the CDTR-PI and three severe events (coagulation disorder, lymphocytosis, and rash by 1 patient each) were reported in the PCN-VK group during the post-treatment period.

Treatment-Related Adverse Events During Treatment

Sixty-five (26%) patients in the CDTR-PI group and 50 (20%) patients in the PCN-VK 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 were diarrhea (11%), nausea (5%) and abdominal pain (4%) in the CDTR-PI group, and nausea (5%), diarrhea (4%) and vaginal moniliasis (4% of females) in the PCN-VK group. The difference in the incidence of treatment-related diarrhea was statistically significant (p = 0.005).

Most treatment-related adverse events in both treatment groups were mild or moderate in intensity. Four severe treatment-related adverse events were reported in the CDTR-PI group (chills, diarrhea, abnormal dreams, and anxiety by 1 patient each) and one severe treatment-related event was reported in the PCN-VK group (diarrhea). A summary of treatment-related adverse events, reported by $\geq$ 3% of patients in either treatment group is presented in Table 33.

Table 33 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=254)					PCN-VK (N=254)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				65	26%				50	20%
BODY AS A WHOLE				16	6%				12	5%
Abdominal pain	5	4	0	9	4%	0	2	0	2	1%
Headache	3	3	0	6	2%	3	4	0	7	3%
DIGESTIVE SYSTEM				45	18%				26	10%
Diarrhea*	16	12	1	29	11%	7	3	1	11	4%
Nausea	7	6	0	13	5%	8	4	0	12	5%
UROGENITAL				N=157					N=171	
SYSTEM (FEMALE)[d]				4	3%				6	4%
Vaginal moniliasis	2	0	0	2	1%	5	1	0	6	4%

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; Mod = moderate; Sev = severe

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[a] Treatment-related adverse events occurring in ≥ 3% of patients in either 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] Female-specific adverse events.

Treatment-Related Adverse Events During Post-treatment

During the post-treatment period, 4 (2%) patients in the CDTR-PI group and 7 (3%) patients in the PCN-VK group reported at least one treatment-related adverse event. Two (1%) female patients in the CDTR-PI group and 1 (1%) female patient in the PCN-VK group reported vaginal moniliasis; all other treatment-related adverse events during the post-treatment period were reported by no more than 1 patient.

ANALYSIS OF ADVERSE EVENTS

All Adverse Events

The most common adverse events in the CDTR-PI and PCN-VK groups were associated with the digestive system (20% and 12%, respectively) and the body as a whole (13% and 15%, respectively). Statistically significant differences were observed between the treatment groups in the incidence of adverse events associated with the digestive system ($p = 0.022$) and the urogenital system ($p = 0.037$). A summary of all adverse events is presented in Table 34.

Table 34 Summary of All Adverse Events Grouped by Body System (During Treatment)

Body System	Number (%) of Patients[a]			
	CDTR-PI (N=254)		PCN-VK (N=254)	
OVERALL[b]	96	(38%)	93	(37%)
Body as a Whole	32	(13%)	37	(15%)
Cardiovascular	4	(2%)	2	(1%)
Digestive*	51	(20%)	31	(12%)
Hemic and Lymphatic	0	(0%)	1	(<1%)
Metabolic and Nutritional Disorders	0	(0%)	1	(<1%)
Musculoskeletal	1	(<1%)	1	(<1%)
Nervous	8	(3%)	16	(6%)
Respiratory	10	(4%)	17	(7%)
Skin and Appendages	14	(6%)	11	(4%)
Special Senses	7	(3%)	7	(3%)
Urogenital (Excluding Female-Specific Events)*	1	(<1%)	8	(3%)
Urogenital (Female)[c]	5	(3%)	7	(4%)

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[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] Female-specific adverse events. Females in CDTR-PI group = 157 and in PCN-VK group = 171.

During the post-treatment period, among patients in the CDTR-PI and PCN-VK groups, adverse events associated with the body as a whole were reported by 13% and 10% of patients, respectively, and adverse events associated with the respiratory system were reported by 5% and 6% of patients, respectively. Female urogenital system events were reported by 3% of females in the CDTR-PI group and 1% of females in the PCN-VK group. All other body system adverse events had an incidence ≤ 2% during the post-treatment period.

Treatment-Related Adverse Events

The most common treatment-related adverse events in the CDTR-PI and PCN-VK groups were associated with the digestive system (18% and 10%, respectively) and the body as a whole (6% and 5%, respectively). A statistically significant difference was observed between the treatment groups in the incidence of adverse events associated with the digestive system ($p = 0.021$). A summary of treatment-related adverse events is presented in Table 35.

Table 35 Summary of Treatment-Related Adverse Events Grouped by Body System (During Treatment)

Body System	Number (%) of Patients[a]			
	CDTR-PI (N=254)		PCN-VK (N=254)	
OVERALL[b]	65	(26%)	50	(20%)
Body as a Whole	16	(6%)	12	(5%)
Cardiovascular	1	(<1%)	1	(<1%)
Digestive*	45	(18%)	26	(10%)
Nervous	7	(3%)	8	(3%)
Respiratory	2	(1%)	0	(0%)
Skin and Appendages	4	(2%)	5	(2%)
Special Senses	1	(<1%)	0	(0%)
Urogenital (Excluding Female-Specific Events)	0	(0%)	4	(2%)
Urogenital (Female)[c]	4	(3%)	6	(4%)

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[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] Female-specific adverse events. Females in CDTR-PI group = 157 and in PCN-VK group = 171.

Adverse Events by Patient Groups

There were no statistically significant treatment differences in the incidence of adverse events during treatment in patient groups categorized by gender, race, and age. The incidence of treatment-related adverse events in these patient groups was also similar in the two treatment groups.

MEDICAL OFFICER'S COMMENTS:

A statistically significant difference was observed in the incidence of treatment-related diarrhea, with 11% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p = 0.005). A statistically significant difference was also observed between the treatment groups in the incidence of treatment-related adverse events associated with the digestive system, with 18% of the CDTR-PI group and 10% of the PCN-VK group reporting this adverse event (p = 0.021).

CONCLUSIONS

The medical officer agrees with the sponsor's conclusions that Cefditoren pivoxil 200 mg BID for 10 days was as effective as Penicillin VK 250 mg QID for 10 days in eradicating S. pyogenes and in resolving the clinical signs and symptoms of streptococcal pharyngitis and/or tonsillitis. The sponsor has provided two adequate and well controlled clinical trials comparing the safety and efficacy of Cefditoren pivoxil with Penicillin VK in the treatment of streptococcal pharyngitis. The two drugs are comparable with regard to clinical and microbiologic cure and both achieve an acceptable cure rate. The safety profile of the two drugs was comparable, except for a slightly higher incidence of diarrhea in patients treated with Cefditoren pivoxil.

REGULATORY RECOMMENDATIONS

Based on the results of the two studies submitted by the sponsor, the medical officer recommends the approval of Cefditoren pivoxil, 250 mg twice a day for 10 days for the treatment of streptococcal pharyngitis.

Sumathi Nambiar, M.D.

Medical Officer

DAIDP, HFD-520

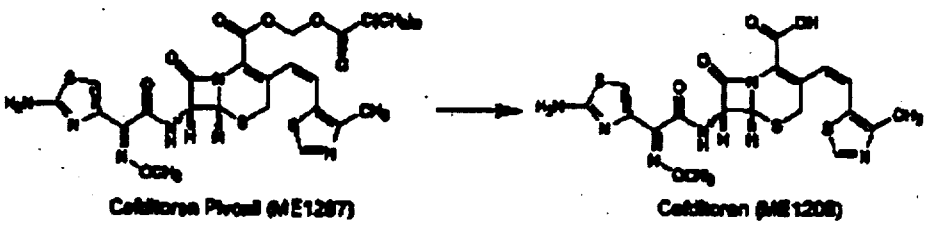
MEDICAL OFFICER REVIEW OF ORIGINAL NDA 21-222:
Review of Acute Bacterial Sinusitis Studies and Review of Safety

Date of Submission: Dec. 28, 1999
Date Review Completed: Dec. 08, 2000

Applicant: TAP Holdings, Inc.
2355 Waukegan Road
Deerfield, IL 60015

DRUG PRODUCT INFORMATION

Established Name: Cefditoren Pivoxil
Trade Name: Spectracef™
Chemical Name: (-)-(6R,7R)-2,2-dimethylproprionyloxymethyl 7-[(Z)-2-(2-amionthiazol-4-yl)-2-methoxyimino acetamido}-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Chem. formula: $C_{25}H_{28}N_6O_7S_3$
Molecular weight: 620.73
Chem. structure:



Drug Category: Cephalosporin antibiotic
Dosage Form: Tablet
Dosage Strength: 200 mg
Route of Administration: Oral

RESUME

Cefditoren (CDTR) is a cephalosporin antibiotic with activity against gram-positive and gram-negative bacteria associated with skin and respiratory tract infections. The active drug, cefditoren, is delivered as a pro-drug, cefditoren pivoxil (CDTR-PI), the pivaloyloxymethyl ester of the active drug. CDTR-PI is hydrolyzed by enzymatic esterases to release the active drug.

TAP Holdings, Inc. submitted studies of the use of CDTR-PI in the treatment of acute bacterial exacerbation of chronic bronchitis, [redacted] streptococcal pharyngitis, and uncomplicated skin and skin structure infections. This document includes an overview of the NDA application for cefditoren pivoxil, an analysis of the indication of [redacted] and a review of the safety of this product. The other indications were reviewed in separate documents.

89 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Addendum to Medical Officer's Review of NDA 21,222 Acute Exacerbation of Chronic Bronchitis Indication

1. General Information

1.1 NDA 21,222

1.2 Applicant Identification

1.2.1 TAP Holdings, Inc.

1.2.2 675 N. Field Drive
Lake Forest, IL 60045
Phone: (847) 236-2524
Fax: (847) 3 17-5795

1.2.3 Jesse Kai Seidman, M.S.
Regulatory Affairs Specialist

1.3 Submission/Review Dates

1.3.1 Date of NDA Submission: December 28, 1999

1.3.2 CDER Stamp Date: December 29, 1999

1.3.3 Date Submission Received by Reviewer: April 4, 2000

1.3.4 Date Review Begun: April 21, 2000

1.3.5 Date Original Review Completed: September 27, 2000

1.3.6 Date Addendum Completed: October 5, 2000
Revised 10/25/00 to reflect additional sensitivity analyses requested by Dr. Murphy on 10/20/00

1.4 Purpose of Addendum: Address Applicant's September 6, 2000 submission and provide additional sensitivity analyses of efficacy data for studies CEF97-003 and CEF97-005.

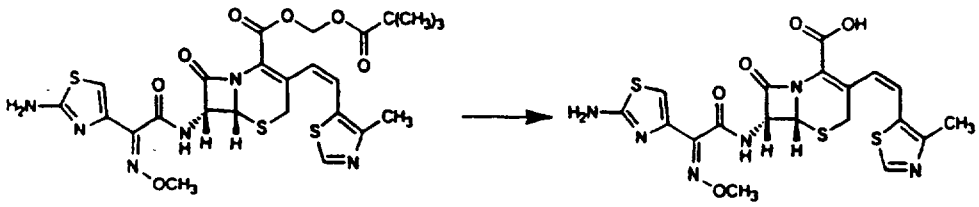
1.5 Drug Identification

1.5.1 Generic Name: Cefditoren pivoxil

1.5.2 Proposed Trade Name: Spectracef TM

1.5.3 Chemical Name: (-)-(6R,7R)-2,2-dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

1.5.4 Chemical Structure:



Cefditoren Pivoxil (CDTR-PI) Cefditoren (CDTR)

1.5.5 Molecular Formula: $C_{25}H_{28}N_6O_7S_3$
1.5.6 Molecular Weight: 620.73

1.6 Pharmacologic Category: Cephalosporin antibiotic

1.7 Dosage Form: Tablet

1.8 Route of Administration: Oral

1.9 Additional Materials Reviewed
September 6, 2000 submission to NDA 21,222 (response to concerns about discordant gram stains, failure to meet entry criteria and statistical plan in submitted and future AECB studies)

2. Background

In the Medical Officer's (MO) and Biostatistician's review of the AECB indication in NDA 21,222 the conclusion reached, based on the MO's evaluability and outcome criteria, was that cefditoren-pivoxil 200 mg PO BID x 10 days should not be approved for the indication of AECB. This recommendation was based on the following findings in the MO's analyses:

- Study CEF97-003 was an underpowered study, but suggested equivalence [97.5% CI –6.2, 26.8] of cefditoren-pivoxil 400 mg PO BID x 10 days (CDTR-PI 400 mg) to cefuroxime 250 mg PO BID x 10 days (CXM-AX) for clinical efficacy in the evaluable population at the Test-of-Cure (TOC) visit. Cefditoren-pivoxil 200 mg PO BID x 10 days (CDTR-PI 200 mg) failed to show equivalence to CXM-AX [97.5% CI –18.8, 13.7] for clinical efficacy in the evaluable population at the Test-of-Cure (TOC) visit.
- Study CEF97-005 failed to show equivalence of CDTR-PI 400 mg [97.5% CI –24.7, 1.5] or CDTR-PI 200 mg [97.5% CI –16.8, 9.1] to clarithromycin 500 mg PO BID x 10 days (CLA) for clinical efficacy in the evaluable population at the TOC visit.

Additionally, based on either the Applicant's analyses or the MO's analyses:

- Study CEF97-003 suggested that CDTR-PI 200 mg was not equivalent to CDTR-PI 400 mg in the clinically evaluable population at the TOC visit (based on Applicant's analysis with statistical adjustment applied for multiple

comparisons {97.5% CI –15.7, 4.0] and the MO's evaluability and outcome criteria [97.5% CI –29.9, 4.2]).

- Study CEF97-005 suggested a trend for patients receiving CDTR-PI 200 mg to have better outcomes than those receiving CDTR-PI 400 mg. This trend is inconsistent with the expected dose response and the findings in study CEF-97-003. The trend for patients in the CDTR-PI 400 mg arm to do worse was not adequately explained by baseline demographic factors, discontinuations due to adverse events, or patient compliance.

In the Applicant's September 6, 2000 submission, at the October 2, 2000 telecon, and at the October 20, 2000 face to face meeting with the Applicant, the Applicant presented arguments supporting their approach to data analyses and expressed that they felt the MO's evaluability and outcome criteria were too strict. In response to the Applicant's concerns additional sensitivity analyses, applying less strict evaluability and outcome criteria have been conducted by the MO and Biostatistician. The Applicant's arguments supporting their data analysis plan and additional analyses conducted by the FDA reviewers are presented where appropriate in the following sections.

3. Regulatory History

Prior minutes of meetings and telecons between the Applicant and Division of Anti-Infective Drug Product (DAIDP) representatives were reviewed. Specific discussions regarding choice of inclusion criteria did not occur between the Applicant and the FDA review team. The only statistical comment that was sent to the Applicant regarding the AECB studies was that a lower bound of delta of 10% should be used to calculate sample sizes.

In order to determine if the Applicant has presented data and data analyses of equivalent regulatory quality to those found in prior approved applications for the indication of AECB, the MO's reviews of NDA 21, 085 (moxifloxacin) and NDA 50,739 (cefdinir) were obtained and reviewed.

A. Moxifloxacin (NDA 21,085)

Two domestic pivotal studies (D96-027 and D96-022) and one European pivotal study (0124) were presented to support an indication of AECB for moxifloxacin. The inclusion criteria for studies D96-027 and D96-022 were more stringent than those of the current application in that they required the presence of purulent sputum and one of the following: increased cough, increased dyspnea, increased sputum volume or fever. Inclusion criteria did not require an adequate gram stain for enrollment. Evaluability criteria differed between the applications in that while a positive sputum culture was not required for a patient to be considered clinically evaluable for moxifloxacin, it was required for a patient to be considered microbiologically evaluable (an adequate gram stain, i.e. > 25

WBC and < 10 epithelial cell per 100x was not required). In validating the data base for moxifloxacin the reviewing MO stated that "the MO evaluated, in a blinded fashion, the response to therapy by examining the five main symptoms that were used to enroll patients in the trial, namely, 1)increased sputum production (necessary to be included in the trial) and 2)cough, 3)dyspnea, 4)sputum thickness/purulence, and 5)fever...The MO agreed with the investigator's assessment of the patient as a clinical success if these particular symptoms were significantly improved from the pre-therapy visit, even if the symptoms did not return to the patient's pre-morbid baseline. If there was no change in any of these symptoms from the pre-therapy visit, the MO graded the patient as a clinical failure regardless of the investigator's assessment." A review of 20% and 10% of CRFs for studies D96-027 and D96-021, respectively, did not show any systematic errors and an analysis of the changes in outcome did not change the overall efficacy analysis, therefore the MO accepted the applicant's assessment of evaluability and outcomes. In addition, a post hoc analysis, by the Applicant showed greater than 98% of patients in each study population met Winnipeg[1] criteria I or II, suggesting they would benefit from antimicrobial treatment of their AECB. Evaluability and efficacy analyses for study D96-027 and D96-021 are provided in Table 1. and Table 2. respectively.

Table 1. Moxifloxacin AECB Study D96-027

	Moxifloxacin 400 mg PO QD x 5 days		Moxifloxacin 400 mg PO QD x 10 days		Clarithromycin 500 mg PO BID x 10days	
	n/N	(%)	n/N	(%)	n/N	(%)
ITT	312/316	(99%)	302/307	(98%)	312/313	(100%)
Clinically Evaluable	250/312	(83%)	256/302	(83%)	251/312	(80%)
Micro Evaluable	143/312	(45%)	148/302	(48%)	129/312	(41%)
Eval Clinical Success at TOC	222/250	(89%)	234/256	(91%)	224/251	(89%)
			95% CI			
Moxifloxacin x 5 days vs Clarithromycin			[-6.1, 4.2]			
Moxifloxacin x 10 days vs Clarithromycin			[-2.7, 7.2]			
Eval Micro Success at TOC	127/143	(89%)	135/148	(91%)	110/129	(85%)
			95% CI			
Moxifloxacin x 5 days vs Clarithromycin			[-3.7, 10.5]			
Moxifloxacin x 10 days vs Clarithromycin			[0.3, 14.5]			

[1] Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106:196-204.

Table 2. Moxifloxacin AECB Study D96-022

	Moxifloxacin 200 mg PO QD x 10 days		Moxifloxacin 400 mg PO QD x 10 days		Cefuroxime axetil 500 mg PO BID x 10days	
	n/N	(%)	n/N	(%)	n/N	(%)
ITT	223/223	(100%)	225/225	(100%)	234/234	(100%)
Clinically Evaluable	177/223	(79%)	170/225	(76%)	185/234	(79%)
Micro Evaluable	77/223	(34%)	73/225	(32%)	85/234	(34%)
Eval Clinical Success at TOC	161/177	(91%)	157/170	(92%)	161/185	(87%)
			95% CI			
Moxifloxacin x 5 days vs Cefuroxime			[-1.6, 11.1]			
Moxifloxacin x 10 days vs Cefuroxime			[-2.5, 10.8]			
Eval Micro Success at TOC	72/77	(94%)	67/73	(92%)	72/85	(85%)
			95% CI			
Moxifloxacin x 5 days vs Cefuroxime			[-1.9, 19.5]			
Moxifloxacin x 10 days vs Cefuroxime			[-4.1, 18.3]			

The European study (#0124) required patients to have 2 of the following 3 signs and symptoms for inclusion: 1)purulent sputum, 2)increased sputum volume, and 3)increased dyspnea. Based on these inclusion criteria only patients meeting Winnipeg criteria Type I or II were enrolled. Validity and outcome criteria were similar to those of D96-027 and D96-022. The MO sampled 10% of CRFs for this study and concluded that there were no systematic errors in the Applicant's analyses and that an analysis of the changes in outcome did not change overall efficacy analyses, therefore the MO accepted the Applicant's assessment of evaluability and outcomes. Evaluability and efficacy analyses for study 0124 are provided in Table 3.

Table 3. Moxifloxacin AECB Study 0124

	Moxifloxacin 400 mg PO QD x 5 days		Clarithromycin 500 mg PO BID x 7 days	
	n/N	(%)	n/N	(%)
Eval Clinical Success at TOC	287/322	(89%)	289/327	(88%)
		95% CI		
Moxifloxacin x 5 days vs Clarithromycin x 7 days		[-3.9, 5.8]		
Eval Micro Success at TOC	89/115	(77%)	71/114	(62%)
		95% CI		
Moxifloxacin x 5 days vs Clarithromycin x 7 days		[3.6, 26.9]		

Medical Officer's Comment: ***The major difference between these studies and the those in the current Application are: 1)more stringent inclusion criteria in the moxifloxacin application regarding signs and symptoms (resulting in most patients meeting Winnipeg Type I or II criteria), 2)investigator's appeared to more closely follow the requirement for all signs and symptoms to be resolved to call a patient a cure (based on MO's core sampling of CRFs), and 3)higher overall cure rates, which may be due to the selection of patients for inclusion who were predicted to be most likely to benefit from antimicrobial therapy. Of note, an investigator (Dr. DeAbate) currently under investigation for trial conduct issues and whose data was excluded from the current application enrolled over 20% of evaluable patients in both study D96-027 and D96-022. The effect of excluding this investigator's data from analyses of the moxifloxacin studies is unknown. Neither these studies nor those in the current Application required sputum samples to be validated by an adequate gram stain.***

B. Cefdinir

One AECB pivotal study (983-5) was presented to support an indication of AECB for moxifloxacin. Data from studies was considered supportive for the indication of AECB, therefore results from one AECB study were considered adequate to support granting the indication. Study 983-5 was conducted at 36 U.S. and international sites. The inclusion criteria differed from those of the current application in that they required the presence of mucopurulent or purulent sputum and productive cough. Inclusion criteria did not require an adequate gram stain for enrollment. Clinical outcome was determined by the recorded signs and symptoms. Although the protocol-specified definition of "cure" for the investigator's assessment of clinical response at the TOC visit was "absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required," the definition of "cure" used in the Applicant's assessment of clinical response at TOC was "$\geq$ 50% decrease in clinical score at TOC relative to baseline." The MO did not comment as to any systematic discrepancies observed between her review of the CRFs and the Applicant's analyses of evaluability and outcome. Evaluability and efficacy analyses according to the Applicant for study 983-5 are provided in Table 4.

Table 4. Cefdinir Evaluability and Efficacy Data for Study 983-5

	Cefdinir 600 mg QD x 10 days		Cefdinir 300 mg BID x 10 days		Cefuroxime 250 mg BID x 10 days	
	n	(%)	n	(%)	n	(%)
ITT	349	(100%)	347	(100%)	349	(100%)
Clinically Evaluable	278	(80%)	286	(82%)	286	(82%)
Clin & Micro Evaluable	119	(34%)	120	(35%)	110	(32%)
Eval Clinical Success at TOC	229/278	(82%)	225/286	(79%)	232/286	(81%)
			95% CI			
Cefdinir 600 mg vs Cefuroxime			[-5.47, 7.98]			
Cefdinir 300 mg vs Cefuroxime			[-9.36, 4.47]			
Eval Clin & Micro Success at TOC	97/119	(82%)	86/120	(72%)	84/110	(76%)
			95% CI			
Cefdinir 600 mg vs Cefuroxime			[-6.29, 16.59]			
Cefdinir 300 mg vs Cefuroxime			[-16.88, 7.49]			

Medical Officer's Comment: ***The major difference between this study and the those in the current Application appears to be override of the investigator's outcome response by criteria applied by the current Applicant to document resolution of signs and symptoms in order to consider a patient a cure.***

4. Sputum Gram Stains

In their September 6, 2000 submission the Applicant provided the reasons they felt patients with sputum gram stains that were inadequate (i.e. not meeting the criteria of > 25 WBC and < 10 epithelial cells per 100x field) at the central lab should be considered evaluable. The Applicant states "looking at the combination of the two studies, 97% (1055/1093) of the pre-therapy Gram stains performed by the clinical sites were reported as good (>25 PMNs and < 10 squamous epithelial cells) while only 68% (742/1093) of the pre-therapy Gram stains fit this criteria when reviewed by the central laboratory. In reviewing the data, it is felt that some of this discrepancy is attributable to sampling error. Different slides prepared from the same sputum sample may contain a variable number of cells, both PMNs and epithelial cells."

Medical Officer's Comment: ***The MO agrees that sampling error may account for some of the observed differences; however, given that the investigators were instructed to swab a purulent appearing area of the sputum specimen and then use this swab to make two slides (one for investigator site and one for central lab), the MO believes this degree of discordant readings to be excessive and that the central lab reading remains the most reliable.***

An additional concern raised by the Applicant's statement is that 38/1093 patients had an inadequate gram stain at the investigator site, yet were still enrolled in the study and considered evaluable if no other evaluability criteria were violated. In the MO's analyses these patients were considered evaluable only if the central lab gram stain result was considered adequate.

If the MO accepts the Applicant's argument that analyses should be based on the investigators gram stain and removes the requirement for gram stain at the central lab be "good" for a patient to be in the MITT population, the MO's revised analyses of clinical outcome are presented in Tables 5. and 6. for CEF97-003 and CEF97-005 respectively.

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Table 5. CEF97-003 Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Original MO analyses						
Post-Therapy						
MITT Cures	71/96	(74%)	71/95	(75%)	85/112	(75%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 12.6]			
CDTR-PI 400 mg vs CXM-AX			[-13.8, 13.3]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-14.9, 13.4]			
Post-Therapy						
Evaluable Cures	66/87	(76%)	66/83	(80%)	78/102	(77%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 13.3]			
CDTR-PI 400 mg vs CXM-AX			[-10.6, 16.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-18.0, 10.6]			
Follow-Up						
MITT Cures	38/96	(40%)	46/95	(48%)	50/112	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-20.4, 10.3]			
CDTR-PI 400 mg vs CXM-AX			[-11.8, 19.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-24.9, 7.2]			
Follow-Up						
Evaluable Cures	37/87	(43%)	46/83	(55%)	46/102	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-18.8, 13.7]			
CDTR-PI 400 mg vs CXM-AX			[-6.2, 26.8]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-29.9, 4.2]			
CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If accept adequate or inadequate gram stain at central lab, but retain other MO criteria.						
Follow-Up						
MITT	59/157	(38%)	74/160	(46%)	75/168	(45%)
Evaluable Cures	58/143	(41%)	71/141	(50%)	71/155	(46%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CXM-AX			[-19.3, 5.1]		[-18.1, 7.6]	
CDTR-PI 400 mg vs CXM-AX			[-10.7, 13.9]		[-8.5, 17.6]	
CDTR-PI 200 mg vs CDTR-PI 400 mg						

Table 6. CEF97-005 Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Original MO Analysis						
Post-Therapy						
MITT Cures	129/165	(78%)	102/156	(65%)	134/173	(78%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-9.4, 10.9]			
CDTR-PI 400 mg vs CLA			[-23.2, -1.0]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[1.6, 24.0]			
Post-Therapy						
Evaluable Cures	115/146	(79%)	95/135	(70%)	122/154	(79%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-11.0, 10.1]			
CDTR-PI 400 mg vs CLA			[-20.3, 2.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 20.0]			
Follow-Up						
MITT Cures	78/165	(47%)	60/156	(39%)	90/173	(52%)
Comparison of Cure Rates			97.5% CI for Difference in Cure Rate[b]			
CDTR-PI 200 mg vs CLA			[-16.9, 7.4]			
CDTR-PI 400 mg vs CLA			[-25.8, 1.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 21.2]			
Follow-Up						
Evaluable Cures	74/146	(51%)	58/135	(43%)	84/154	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.8, 9.1]			
CDTR-PI 400 mg vs CLA			[-24.7, 1.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-5.6, 21.0]			
CDTR-PI = cefditoren pivoxil; CLA = clarithromycin n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If accept adequate or inadequate gram stain at central lab, but retain MO's other criteria						
Follow-Up						
MITT	103/233	(44%)	94/227	(41%)	116/240	(48%)
Evaluable Cures	97/205	(47%)	89/198	(45%)	109/212	(51%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CLA			[-14.4, 6.1]		[-15.1, 6.9]	
CDTR-PI 400 mg vs CLA			[-17.2, 3.4]		[-17.5, 4.6]	
CDTR-PI 200 mg vs CDTR-PI 400 mg						

The Applicant went on to state that the majority of patients with inadequate gram stains (66%, 231/351) "had a result of >25 PMNs and > 10 squamous epithelial cells (as read by the central laboratory, conflicting with the readings of the site which determined that their slides demonstrated > 25 PMNs and < 10 squamous epithelial cells). These patients had a sufficient number of PMNs present to indicate an infection as assessed by both the clinical site and the central laboratory and were determined to have < 10 squamous epithelial cells on the slide reviewed by the clinical sites. In addition, the cultures from the majority of patients (75%,

173/231 yielded only one pathogen. Sampling error is possible given that the resulting culture yielded an acceptable respiratory pathogen. Therefore, the potential for contamination, as perhaps determined by the presence of greater than 10 squamous epithelial cells, does not apply."

Medical Officer's Comment: ***The MO agrees that patients with > 25 PMNs regardless of the number of epithelial cells would have had a purulent appearing sputum. However, the presence of < 10 epithelial cells supports the specimen represents a lower respiratory tract specimen, while the presence of > 10 epithelial cells suggests the specimen arose in the upper respiratory tract. In a study enrolling patients whose upper and lower respiratory tracts are frequently colonized with common respiratory pathogens, it is not unexpected for cultures to have shown growth of one pathogen regardless of their origin.***

The MO has reexamined gram stain findings for the core sample (90/618 CRFs) for study CEF97-003 and found that 39% (35/90) of patients had inadequate or missing gram stains at the central lab, 20% (18/90) had gram stains with > 25 PMNs and > 10 epithial cells on gram stains, and 13% (12/90) *had > 25 PMNs and > 10 epithial cells on gram stains and one "respiratory* ***pathogen" on culture. Of*** *concern, these 12 culture reports documented* ***additional culture findings, which include "normal respiratory flora" (S. viridans, Neisseria species, Micrococcus species, etc.), yeast, and other potential pathogens with growth of less than 3+ (the criteria used to consider growth of a pathogen in these protocols).***

However, if it is accepted that patients with gram stains demonstrating > 25 PMNs and > 10 epithelial cells and a "single pathogen" on culture (49%, 173/351) should be valid for efficacy analyses, 51% (178/351) of patients with inadequate gram stains remain unevaluable. The SAS data set previously provided to the FDA reviewers by the Applicant records central laboratory gram stains in a binary fashion (either "good" or not good), therefore reanalyses based on these criteria were not possible.

5. Signs and Symptoms Supporting the Diagnosis of AECB

In their September 6, 2000 submission the Applicant attempted to address the MO's concern that some patients did not meet the entry criteria of having at least two signs and symptoms consistent with a diagnosis of an acute exacerbation of chronic bronchitis as required in the inclusion criteria. The Applicant stated that viewing the combined results of the pivotal studies "of 1106 patients, 27 patients did not show a worsening of at least two signs and symptoms from the pre-exacerbation to the pre-therapy assessment." The Applicant stated, however, that 25 of these 27 patients showed an "improvement from the pre-therapy assessment to the post and/or follow-up assessments, though, indicating they were experiencing an exacerbation at the time of enrollment into the study." The