# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-222**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Review of the Skin and Skin Structure Infection Indication

**NDA:** 21-222

**Date of Submission:** December 28, 1999

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**Date of Review:** May 12, 2000

**Applicant:** Tap Holdings, Inc.

**Drug-Generic:** Cefditoren Pivoxil
**Trade:** Spectracef™
**Class:** Cephalosporin

## Executive Summary

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* or *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 in eradication rates between 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%), in the cefditoren 200 mg, cefditoren 400 mg, and cefuroxime groups, 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 sponsor's results for these groups. Some major differences between the results occurred, which required the sponsor to re-analyze some of the data from both studies.

Two major issues developed concerning the differences between the results of the applicant and FDA's analysis. 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 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 subsequently submitted the results to the application. 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. 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 experienced more adverse reactions than those who received the lower dose did. 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.

The applicant has submitted sufficient data from two clinical studies to show that cefditoren is safe and effective in the treatment of uncomplicated skin and skin structure infections in an adult population. Data from both 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.

Therefore, it is recommended that Spectracef (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.*

# Clinical Review of Studies for Skin and Skin Structure Infections (SSSI)

**Indication:** Uncomplicated Skin and Skin Structure Infections.

**Title and Study Number:** Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefuroxime Axetil in the Treatment of Patients with Uncomplicated Skin or Skin Structure Infections (Protocol No. Cef-97-009).

**Objective:** To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and cefuroxime axetil 250 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 cefuroxime axetil 250 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:** (as duplicated from the Applicant's submission)

**Population:** – Males and females ≥12 years of age and weighing at least 34 kilograms (75 pounds) were enrolled if they had a diagnosis of skin or skin structure infection that was suitable for oral antibiotic therapy and were not seriously ill.

**Inclusion Criteria:**

Patients were required to meet all of the following criteria to be considered for inclusion in the study:

- Diagnosed as having a mild to moderate skin or skin structure bacterial infection suitable for oral antibiotic therapy based on the following evidence:

- Whenever possible, a specimen of culturable material from the site of infection was to be obtained within 48 hours prior to initiation of study drug therapy for culture.
- Two or more of the following local signs and symptoms of skin or skin structure infection:

| | |
|---|---|
| pain | purulent drainage/discharge |
| tenderness | induration |
| swelling | regional lymph node swelling |

erythema regional lymph node tenderness

associated warmth

- Acceptable skin or skin structure infections included but were not limited to: cellulitis, erysipelas, impetigo, carbunculosis, simple abscess, wound infection, infected sebaceous cyst, furunculosis, and folliculitis.
- Was 12 years of age or older, and weighed at least 34 kilograms (75 pounds).
- Female patients were to be non-lactating and at no risk of pregnancy (i.e., post-menopausal for at least 1 year, hysterectomized, or had tubal ligation). A female patient with childbearing potential could be enrolled provided she had a negative prestudy urine and/or serum human chorionic gonadotropin (hCG) pregnancy test and would utilize oral contraceptives, intrauterine device (IUD), Depo Provera, Norplant, or barrier contraceptive methods throughout the study. If oral contraceptives, Depo Provera, or Norplant were used, the patient must have taken the contraceptive for at least 3 months prior to study entry.
- Voluntarily signed a consent form after the nature of the study was explained. If the patient was not of legal age, the consent form was to be signed by both the patient and the parent or legal guardian.

**Exclusion Criteria:**

Patients were excluded from enrollment for any of the following reasons:

- History of hypersensitivity to penicillin, cephalosporins, or β–lactam antibiotics.
- Chronic or underlying skin condition at the site of infection (e.g., a secondarily infected atopic dermatitis or eczema) or infections involving prosthetic materials (e.g., catheter tunnel infections, orthopedic hardware).
- A wound secondary to thermal injury or acne vulgaris.
- Any site of infection that required surgical debridement or incision and drainage of the infected area, or excision of infected lesions (or body parts).
- Any infection that necessitated the use of concomitant oral or parenteral antibiotic therapy.
- Treatment with a systemic antibiotic within 7 days prior to study drug administration or treatment with a long-acting injectable antibiotic (e.g., penicillin G benzathine) within 30 days prior to study drug administration.
- Treatment with azithromycin within 2 weeks prior to study drug administration.
- Treatment with an investigational drug within 4 weeks prior to study drug administration.
- Previous treatment in the current study.

- Underlying condition/disease that would be likely to interfere with completion of the course of study drug therapy or follow-up.

- Known significant renal or hepatic impairment indicated by recent chemistries:
  serum creatinine > 2.0 mg/dL
  AST > 2 X the upper limit of normal
  ALT > 2 X the upper limit of normal
  alkaline phosphatase > 1.25 X the upper limit of normal
  total bilirubin > 2 X the upper limit of normal
  blood urea nitrogen (BUN) ≥ 30 mg/dL.

- Immunocompromised host status.

- Currently receiving or likely to require other concomitant systemic antimicrobial therapy

- Currently receiving or likely to require any other investigational agent or corticosteroid medication (≥10 mg/day prednisone or equivalent) during the period between the Pre-Therapy Visit (initial presentation to office/clinic) and the Follow-Up Visit (7 to 14 days posttreatment).

- Concomitant topical therapy (e.g., corticosteroids or antimicrobials) at the site of infection.

- Receiving chronic treatment with an anticoagulant (chronic aspirin use up to 325 mg/day was acceptable).

- Documented or suspected bacteremia.

- Infections of the nail beds and scalp.

- Diabetes mellitus (Type I and Type II).
- Significant vascular disease.

- Patients with abscesses in an anatomical site, such as the rectal area, where the risk of anaerobic pathogen involvement was higher.

- Isolated (one solitary area of infection) furunculosis or folliculitis.

**Clinical Reviewer's Note:** *Both the patient inclusion and exclusion criteria are consistent with the guidelines developed by the DAIDP.*

**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.*

**Endpoints Defined (Clinical and Microbiological)**

The schedule of visits, examinations and evaluations for the patients in this study is shown in Table 1.

Table 1. 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.

**Clinical Reviewer's Note:** *The criteria are acceptable.*

**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 cefuroxime axetil 250 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 cefditoren 400 mg treatment group and the cefuroxime treatment group; however, all pairwise comparisons were performed for all efficacy and safety analyses. All analyses were performed using SAS®, Version 6.12 ( 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 enrolled in each of the treatment arms by each investigator.



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**Table 2. Distribution of All Enrolled Patients by Investigator**

| Investigator | Site | Treatment Group CDTR-PI 200 mg | CDTR-PI 400 mg | CXM-AX 250 mg |
|---|---|---|---|---|
| Abraham | Berkeley Heights, NJ | 1 | 1 | 1 |
| Altamura | Mesa, AZ | 1 | 0 | 1 |
| Alwine | Downington, PA | 5 | 6 | 6 |
| Asher | Nashville, TN | 3 | 2 | 2 |
| Baker | Bakersfield, CA | 1 | 0 | 0 |
| Baz | Fresno, CA | 0 | 1 | 1 |
| Block | Bardstown, KY | 1 | 1 | 1 |
| Burnett | Atlanta, GA | 1 | 0 | 1 |
| Campitelli | West Palm Beach, FL | 6 | 7 | 6 |
| Campos | Houston, TX | 5 | 6 | 5 |
| Casale | Papillion, NE | 2 | 1 | 2 |
| Champlin | Carmichael, CA | 9 | 9 | 8 |
| Coalson | Beaver Creek, OH | 17 | 17 | 17 |
| Cole | Long Beach, CA | 1 | 0 | 1 |
| Condemi | Rochester, NY | 1 | 0 | 1 |
| Drehobl | San Diego, CA | 6 | 5 | 5 |
| Faircloth | Birmingham, AL | 3 | 3 | 2 |
| Faust | Indianapolis, IN | 4 | 4 | 3 |
| Fling | Fort Worth, TX | 0 | 1 | 1 |
| Forsha | Salt Lake City, UT | 4 | 3 | 4 |
| Garrison | Montgomery, AL | 19 | 18 | 18 |
| Gezon | Salt Lake City, UT | 6 | 5 | 6 |
| Goffe | Seattle, WA | 1 | 1 | 1 |
| Goldstein | Palm Harbor, FL | 1 | 1 | 2 |
| Green | Hampton, VA | 6 | 6 | 7 |
| Hebert | Houston, TX | 3 | 4 | 4 |
| Honsinger | Los Alamos, NM | 3 | 3 | 2 |
| Kivitz | Altoona, PA | 1 | 0 | 1 |
| Larsen L. | Salt Lake City, UT | 2 | 2 | 2 |
| Larsen S. | Middletown, NJ | 7 | 8 | 8 |
| Lutarewych | Fort Myers, FL | 3 | 3 | 3 |
| Maggiacomo | Cranston, RI | 2 | 2 | 1 |
| Markunas | Burlington, NJ | 8 | 9 | 7 |
| McAdoo | Milan, TN | 5 | 4 | 5 |
| McCulloch | Eclectic, AL | 2 | 1 | 1 |
| McLaren | St. Louis, MO | 2 | 1 | 1 |
| Millikan | New Orleans, LA | 10 | 10 | 9 |
| Miskin | West Palm Beach, FL | 9 | 9 | 9 |
| Muchmore | Oklahoma City, OK | 0 | 0 | 1 |
| Muluk | Pittsburgh, PA | 0 | 1 | 0 |
| Munoz | Tacoma, WA | 9 | 8 | 7 |
| Newman | Oceanside, CA | 8 | 8 | 7 |
| Paster | Oregon, WI | 10 | 9 | 10 |
| Pittman | Oklahoma City, OK | 2 | 1 | 1 |
| Puopolo | Milford, MA | 3 | 4 | 3 |
| Rafal | East Setauket, NY | 2 | 2 | 1 |
| Ramirez | Louisville, KY | 2 | 2 | 1 |
| Resnick | Lake Jackson, TX | 9 | 9 | 10 |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

**Table 2. Distribution of All Enrolled Patients by Investigator (continued)**

| Investigator | Site | Treatment Group CDTR-PI 200 mg | CDTR-PI 400 mg | CXM-AX 250 mg |
|---|---|---|---|---|
| Rist | Knoxville, TN | 5 | 5 | 6 |
| Romney | Salt Lake City, UT | 2 | 2 | 2 |
| Rubino | Raleigh, NC | 3 | 3 | 3 |
| Russell | Tallassee, AL | 3 | 4 | 4 |
| Savin | Lake Bluff, IL | 2 | 1 | 2 |
| Schoch | Austin, TX | 1 | 1 | 1 |
| Sievers | Kettering, OH | 11 | 11 | 11 |
| Storfer | St. Louis, MO | 6 | 5 | 6 |
| Taylor | Miami, FL | 1 | 0 | 1 |
| Tucker | Wenatchee, WA | 9 | 9 | 8 |
| Warren | Jackson, TN | 1 | 3 | 2 |
| White | Lexington, TN | 7 | 7 | 8 |
| Williams C. | Vero Beach, FL | 25 | 26 | 25 |
| Williams, II | Trenton, TN | 5 | 4 | 4 |
| Yeoman | Philadelphia, PA | 4 | 4 | 4 |
| | **TOTAL** | **291** | **283** | **283** |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

**Patient Demographics:** The patient demographics for all patients according to the sponsor are summarized in Table 3.

**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 3. Demographic Information (All Patients)**

| Demographic Characteristic | Number of Patients by Treatment Group: CDTR-PI 200 mg BID | CDTR-PI 400 mg BID | CXM-AX 250 mg BID | P-value[a] |
|---|---|---|---|---|
| Total Treated | 291 | 283 | 283 | |
| Gender | | | | 0.409 |
| Female | 138 (47%) | 142 (50%) | 150 (53%) | |
| Male | 153 (53%) | 141 (50%) | 133 (47%) | |
| Race[b] | | | | 0.375 |
| Caucasian | 227 (78%) | 234 (83%) | 230 (81%) | |
| Black | 42 (14%) | 38 (13%) | 35 (12%) | |
| Hispanic | 15 ( 5%) | 8 ( 3%) | 14 ( 5%) | |
| Asian | 4 ( 1%) | 0 ( 0%) | 1 (<1%) | |
| Other | 3 ( 1%) | 3 ( 1%) | 3 ( 1%) | |
| Age (years)[c] | | | | 0.966 |
| <45 | 181 (62%) | 181 (64%) | 175 (62%) | |
| 45 - 65 | 83 (29%) | 66 (23%) | 76 (27%) | |
| >65 | 27 ( 9%) | 36 (13%) | 32 (11%) | |
| Mean (SD) | 40.9 (17.3) | 40.8 (17.9) | 41.2 (18.0) | |
| Range | 13-87 | 12-93 | 12-92 | |
| Weight (pounds)[c] | | | | 0.683 |
| <135 | 39 (13%) | 49 (17%) | 54 (19%) | |
| 135 - 165 | 76 (26%) | 77 (27%) | 74 (26%) | |
| 166 - 195 | 78 (27%) | 63 (22%) | 71 (25%) | |
| >195 | 94 (32%) | 92 (33%) | 82 (29%) | |
| Missing | 4 ( 1%) | 2 ( 1%) | 2 ( 1%) | |
| Mean (SD) | 181.1 (45.5) | 181.5 (51.4) | 178.1 (50.7) | |
| Range | 95-341 | 99-388 | 95-430 | |
| Height (inches)[c] | N=291 | N=282 | N=281 | 0.642 |
| Mean (SD) | 67.4 (4.1) | 67.1 (4.2) | 67.1 (4.1) | |
| Range | 56-77 | 50-78 | 57-77 | |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; 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 observed (Table 4). The most common diagnoses were cellulitis (28% of patients), wound infection (25%), and simple abscess (17%). The majority of patients had a moderate infection (63%) and were considered to be in good clinical condition (83%). Table 4 summarizes the baseline characteristics for all patients by treatment group.

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

**Table 4. Summary of Baseline Characteristics (All Patients)**

| Baseline Characteristics | Number of Patients by Treatment Group: CDTR-PI 200 mg BID | CDTR-PI 400 mg BID | CXM-AX 250 mg BID | P-value[a] |
|---|---|---|---|---|
| Total Treated | 291 | 283 | 283 | |
| Diagnosis[b] | | | | 0.481 |
| Cellulitis | 80 (27%) | 74 (26%) | 87 (31%) | |
| Wound infection | 77 (26%) | 59 (21%) | 76 (27%) | |
| Folliculitis | 20 ( 7%) | 28 (10%) | 22 ( 8%) | |
| Simple abscess | 53 (18%) | 50 (18%) | 40 (14%) | |
| Infected sebaceous cyst | 26 ( 9%) | 35 (12%) | 21 ( 7%) | |
| Impetigo | 19 ( 7%) | 21 ( 7%) | 18 ( 6%) | |
| Furunculosis | 10 ( 3%) | 12 ( 4%) | 12 ( 4%) | |
| Other (erysipelas, carbunculosis, etc.) | 6 ( 2%) | 4 ( 1%) | 7 ( 2%) | |
| Infection Status | | | | 0.951 |
| Mild | 93 (32%) | 91 (32%) | 96 (34%) | |
| Moderate | 188 (65%) | 180 (64%) | 174 (61%) | |
| Severe | 10 ( 3%) | 12 ( 4%) | 13 ( 5%) | |
| Clinical Condition | | | | 0.162 |
| Good | 233 (80%) | 243 (86%) | 234 (83%) | |
| Fair | 57 (20%) | 40 (14%) | 47 (17%) | |
| Poor | 1 (<1%) | 0 ( 0%) | 2 ( 1%) | |
| Smoking Status | | | | 0.402 |
| Non-smoker | 155 (53%) | 144 (51%) | 146 (52%) | |
| Smoker | 103 (35%) | 99 (35%) | 111 (39%) | |
| Ex-smoker | 33 (11%) | 40 (14%) | 26 ( 9%) | |
| Alcohol Use | | | | 0.309 |
| Non-drinker | 154 (53%) | 146 (52%) | 132 (47%) | |
| Drinker | 122 (42%) | 129 (46%) | 139 (49%) | |
| Ex-drinker | 15 ( 5%) | 8 ( 3%) | 12 ( 4%) | |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

[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.

[b] P-value from Chi-square test after combining furunculosis, erysipelas, carbunculosis, and other.

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

**Table 5. Duration of Treatment and Study Drug Compliance (Evaluable Patients)**

| | CDTR-PI 200 mg BID N=265 | | CDTR-PI 400 mg BID N=257 | | CXM-AX 250 mg BID N=265 | | P-value[a] |
|---|---|---|---|---|---|---|---|
| Total Treated | | | | | | | |
| Treatment Duration (days) | | | | | | | 0.317 |
| <4 | 2 | (1%) | 9 | ( 4%) | 4 | ( 2%) | |
| 4 – 7 | 6 | (2%) | 5 | ( 2%) | 8 | ( 3%) | |
| 8 – 10 | 178 | (67%) | 163 | (63%) | 180 | (68%) | |
| >10 | 79 | (30%) | 80 | (31%) | 73 | (28%) | |
| Mean (SD) | 10.2 | (1.2) | 10.0 | (1.7) | 10.0 | (1.4) | |
| Min – Max | [redacted] | | | | | | |
| Compliance[b] (percentage) | | | | | | | 0.263 |
| <80 | 8 | ( 3%) | 15 | ( 6%) | 12 | ( 5%) | |
| 80 – 90 | 15 | ( 6%) | 16 | ( 6%) | 17 | ( 6%) | |
| >90 | 242 | (91%) | 226 | (88%) | 236 | (89%) | |
| Mean (SD) | 97.3 | (10.7) | 95.3 | (15.8) | 96.3 | (13.8) | |
| Min – Max | [redacted] | | | | | | |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; 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.*

**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.

**Clinical Reviewer's Note:** *Of the 291 patients enrolled in the 200 mg cefditoren group, 135 (46%) patients were evaluable for both a clinical and microbiological analysis. In the 400 mg cefditoren group, 143 (51%) of the 283 enrolled patients were evaluable for both analyses. For the cefuroxime group, 121/283 (43%) were evaluable. The groups do appear to be roughly comparable; however, a slightly higher percentage of patients in the cefditoren arms were both clinically and microbiologically evaluable compared to the cefuroxime group.*

**Table 6. Disposition of Patients by Data Set**

| | CDTR-PI 200 mg BID | CDTR-PI 400 mg BID | CXM-AX 250 mg BID |
|---|---|---|---|
| All Patients: Randomized and Received Study Drug | 291 | 283 | 283 |
| Included in Clinically Evaluable Efficacy Analyses: | | | |
| Post-Therapy | 257 | 254 | 258 |
| Follow-Up | 265 | 257 | 265 |
| Excluded at Post-Therapy: | 34 | 29 | 25 |
| No clinical response assessed within visit window | 22 | 15 | 17 |
| Received less than 80% of study drug | 3 | 6 | 3 |
| Received less than 2 consecutive days of study drug | 4 | 4 | 3 |
| Lost to follow-up | 3 | 0 | 1 |
| Admission criteria not met | 2 | 1 | 1 |
| Received additional antimicrobials | 0 | 3 | 0 |
| Excluded at Follow-Up: | 26 | 26 | 18 |
| No clinical response assessed within visit window | 14 | 11 | 9 |
| Received less than 80% of study drug | 2 | 6 | 2 |
| Received less than 2 consecutive days of study drug | 4 | 4 | 3 |
| Lost to follow-up | 3 | 0 | 1 |
| Admission criteria not met | 2 | 1 | 1 |
| Received additional antimicrobials | 1 | 4 | 2 |
| Included in Microbiologically Evaluable Efficacy Analyses: | | | |
| Post-Therapy | 131 | 137 | 119 |
| Follow-Up | 135 | 143 | 121 |
| Excluded at Post-Therapy: | 160 | 146 | 164 |
| No causative skin pathogen isolated pretreatment | 140 | 129 | 154 |
| No culture obtained within visit window | 9 | 11 | 6 |
| Received less than 80% of study drug | 2 | 3 | 2 |
| Received less than 2 consecutive days of study drug | 4 | 2 | 1 |
| Lost to follow-up | 3 | 0 | 1 |
| Admission criteria not met | 2 | 0 | 0 |
| Received additional antimicrobials | 0 | 1 | 0 |
| Excluded at Follow-Up: | 156 | 140 | 162 |
| No causative skin pathogen isolated pretreatment | 140 | 129 | 154 |
| No culture obtained within visit window | 6 | 6 | 5 |
| Received less than 80% of study drug | 1 | 2 | 0 |
| Received less than 2 consecutive days of study drug | 4 | 2 | 1 |
| Lost to follow-up | 3 | 0 | 1 |
| Admission criteria not met | 2 | 0 | 0 |
| Received additional antimicrobials | 0 | 1 | 1 |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

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## 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 7. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 230/257 | (89%) | 225/254 | (89%) | 232/258 | (90%) |
| Failure | 27/257 | (11%) | 29/254 | (11%) | 26/258 | (10%) |

| Comparison of Cure Rates | P-value[a] | 95% CI for Difference in Cure Rate[b] |
|---|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.886 | [-5.7, 4.8] |
| CDTR-PI 400 mg vs CXM-AX | 0.670 | [-6.7, 4.0] |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | 0.778 | [-4.5, 6.3] |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
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 8. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 223/265 | (84%) | 216/257 | (84%) | 234/265 | (88%) |
| Failure | 42/265 | (16%) | 41/257 | (16%) | 31/265 | (12%) |

| Comparison of Cure Rates | P-value[a] | 95% CI for Difference in Cure Rate[b] |
|---|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.207 | [-10.0, 1.7] |
| CDTR-PI 400 mg vs CXM-AX | 0.165 | [-10.2, 1.7] |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | >0.999 | [ -6.2, 6.4] |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
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.

**Table 9. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 112/131 | (85%) | 112/137 | (82%) | 103/119 | (87%) |
| Mixed[a] | 3/131 | (2%) | 9/137 | ( 7%) | 6/119 | ( 5%) |
| Failure | 16/131 | (12%) | 16/137 | (12%) | 10/119 | ( 8%) |

| Comparison of Cure Rates | P-value[b] | 95% CI for Difference in Cure Rate[c] |
|---|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.857 | [ -9.7, 7.5] |
| CDTR-PI 400 mg vs CXM-AX | 0.311 | [-13.7, 4.1] |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | 0.416 | [ -5.1, 12.6] |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
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 10. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 110/135 | (81%) | 121/143 | (85%) | 103/121 | (85%) |
| Mixed[a] | 1/135 | (1%) | 2/143 | (1%) | 5/121 | (4%) |
| Failure | 24/135 | (18%) | 20/143 | (14%) | 13/121 | (11%) |

| Comparison of Cure Rates | P-value[b] | 95% CI for Difference in Cure Rate[c] |
|---|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.504 | [-12.8, 5.5] |
| CDTR-PI 400 mg vs CXM-AX | >0.999 | [ -9.2, 8.2] |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | 0.524 | [-12.0, 5.7] |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
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 at the Follow-up visit were 110/135 (81%) for the 200 mg cefditoren group, 121/143 (85%) for the 400 mg cefditoren group, and 103/121 (85%) for the cefuroxime group.

**Clinical cure rates by Diagnosis:** The applicant 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, except folliculitis, impetigo, and infected sebaceous cysts appear to be comparable to the cure rates for the comparator drug. No explanation was provided by the applicant concerning the study drug's poor performance in the three aforementioned skin infections.*

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Table 11. CLINICAL CURE RATE BY BASELINE DIAGNOSIS AT THE POST- THERAPY VISIT
EVALUABLE PATIENTS
CEF- 97- 009

| | CEFDITOREN PIVOXIL == 200 MG BID == | | CEFDITOREN PIVOXIL == 400 MG BID == | | CEFUROXIME AXETIL == 500 MG BID == | |
|---|---|---|---|---|---|---|
| BASELINE DIAGNOSIS | n/N | PCT | n/N | PCT | n/N | PCT |
| CELLULITUS | 67/72 | 93% | 56/66 | 85% | 72/80 | 90% |
| FOLLICULITIS | 16/19 | 84% | 27/27 | 100% | 19/21 | 90% |
| FURUNCULOSIS | 7/8 | 88% | 11/11 | 100% | 8/11 | 73% |
| SIMPLE ABSCESS | 43/46 | 93% | 41/45 | 91% | 35/38 | 92% |
| IMPETIGO | 16/19 | 84% | 14/19 | 74% | 14/15 | 93% |
| INFECTED SEBACEOUS CYST | 14/21 | 67% | 25/30 | 83% | 17/19 | 89% |
| WOUND INFECTION | 63/67 | 94% | 48/53 | 91% | 60/67 | 90% |
| ERYSIPELAS | 1/1 | 100% | 0/0 | | 2/2 | 100% |
| CARBUNCULOSIS | 2/2 | 100% | 2/2 | 100% | 2/2 | 100% |
| OTHER | 1/2 | 50% | 1/1 | 100% | 3/3 | 100% |
| ACROSS DIAGNOSIS | 230/257 | 89% | 225/254 | 89% | 232/258 | 90% |

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

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Table 12. CLINICAL CURE RATE BY BASELINE DIAGNOSIS AT THE FOLLOW- UP VISIT
EVALUABLE PATIENTS
CEF- 97- 009

| BASELINE DIAGNOSIS | CEFDITOREN PIVOXIL == 200 MG BID == n/N | PCT | CEFDITOREN PIVOXIL == 400 MG BID == n/N | PCT | CEFUROXIME AXETIL == 500 MG BID == n/N | PCT |
|---|---|---|---|---|---|---|
| CELLULITUS | 66/75 | 88% | 54/66 | 82% | 69/79 | 87% |
| FOLLICULITIS | 12/19 | 63% | 23/27 | 85% | 20/22 | 91% |
| FURUNCULOSIS | 7/8 | 88% | 11/11 | 100% | 8/11 | 73% |
| SIMPLE ABSCESS | 42/46 | 91% | 38/46 | 83% | 36/40 | 90% |
| IMPETIGO | 13/19 | 68% | 13/19 | 68% | 16/18 | 89% |
| INFECTED SEBACEOUS CYST | 16/23 | 70% | 25/30 | 83% | 17/19 | 89% |
| WOUND INFECTION | 64/70 | 91% | 48/54 | 89% | 61/69 | 88% |
| ERYSIPELAS | 0/1 | 0% | 0/0 | | 2/2 | 100% |
| CARBUNCULOSIS | 2/2 | 100% | 3/3 | 100% | 2/2 | 100% |
| OTHER | 1/2 | 50% | 1/1 | 100% | 3/3 | 100% |
| ACROSS DIAGNOSIS | 223/265 | 84% | 216/257 | 84% | 234/265 | 88% |

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

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## Microbiology

Table 13 shows the eradication rates for the sponsor's proposed pathogens at the Post-Therapy visit for all three treatment groups.

**Table 13. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| OVERALL | 158/182 | ( 87%) | 163/193 | ( 84%) | 155/175 | ( 89%) |
| *S. aureus* | 70/79 | ( 89%) | 69/82 | ( 84%) | 63/66 | ( 95%) |
| *S. pyogenes* | 11/11 | (100%) | 8/8 | (100%) | 6/6 | (100%) |
| *P. magnus* | 14/17 | ( 82%) | 21/25 | ( 84%) | 17/21 | ( 81%) |
| *E. faecalis* | 9/11 | ( 82%) | 10/13 | ( 77%) | 10/14 | ( 71%) |
| *S. agalactiae* | 2/2 | (100%) | 9/9 | (100%) | 10/10 | (100%) |
| *P. aeruginosa* | 8/8 | (100%) | 4/5 | ( 80%) | 4/6 | ( 67%) |
| *P. asaccharolyticus* | 2/3 | ( 67%) | 7/10 | ( 70%) | 5/5 | (100%) |
| *E. cloacae* | 5/6 | ( 83%) | 4/6 | ( 67%) | 3/4 | ( 75%) |
| *E. coli* | 4/4 | (100%) | 3/4 | ( 75%) | 5/7 | ( 71%) |
| *Bacteroides* spp. | 6/7 | ( 86%) | 7/7 | (100%) | 10/11 | ( 91%) |

| Comparison of Overall Eradication Rates | P-value[a] |
|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.633 |
| CDTR-PI 400 mg vs CXM-AX | 0.287 |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | 0.558 |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] P-value for comparison between treatment groups using Fisher's exact test.

In the 200 mg cefditoren group, 158 of 182 (87%) isolates were eradicated, while 163 of 193 (84%) isolates in the 400 mg cefditoren group were eradicated at the Post-Therapy Visit. For the comparator drug cefuroxime, 155 of 175 (89%) isolates were eradicated.

**Clinical Reviewer's Note:** *The applicant has provided data regarding the eradication rates of all causative skin pathogens, including both S. aureus and S. pyogenes. Since the protocol and the FDA 's guidance document specify these two organisms as target pathogens for the skin and skin structure infection indication, it is more important to compare the eradication rates for these two species across the three treatment groups. The eradication rates for S. aureus among these three groups were as follows: 70 out of 79 (89%) in the 200 mg cefditoren, 69 out of 82 (84%) in the 400 mg cefditoren group, and 63 out of 66 (95%) in the cefuroxime group. For S. pyogenes, the eradication rates were higher at 11/11 (100%), 8/8 (100%), and 6/6 (100%), respectively. The comparator drug cefuroxime performed better than either dose of the study drug in both the overall eradication rate of all skin pathogens and the eradication rate for S. aureus.*

The eradication rates at the Follow-Up visit are shown in the following table.

**Table 14. 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 (%) | | CXM-AX 250 mg BID n/N (%) | |
|---|---|---|---|---|---|---|
| OVERALL | 152/188 | ( 81%) | 172/203 | ( 85%) | 156/176 | ( 89%) |
| *S. aureus* | 67/81 | ( 83%) | 76/87 | ( 87%) | 59/67 | ( 88%) |
| *S. pyogenes* | 9/10 | ( 90%) | 9/10 | ( 90%) | 6/6 | (100%) |
| *P. magnus* | 16/19 | ( 84%) | 22/26 | ( 85%) | 17/21 | ( 81%) |
| *E. faecalis* | 10/12 | ( 83%) | 11/13 | ( 85%) | 12/15 | ( 80%) |
| *S. agalactiae* | 2/3 | ( 67%) | 9/10 | ( 90%) | 8/9 | ( 89%) |
| *P. aeruginosa* | 6/8 | ( 75%) | 4/5 | ( 80%) | 3/5 | ( 60%) |
| *P. asaccharolyticus* | 1/3 | ( 33%) | 7/10 | ( 70%) | 5/5 | (100%) |
| *E. cloacae* | 5/6 | ( 83%) | 4/6 | ( 67%) | 3/4 | ( 75%) |
| *E. coli* | 4/4 | (100%) | 3/4 | ( 75%) | 7/7 | (100%) |
| *Bacteroides* spp. | 5/7 | ( 71%) | 7/7 | (100%) | 11/11 | (100%) |

| Comparison of Overall Eradication Rates | P-value[b] |
|---|---|
| CDTR-PI 200 mg vs CXM-AX | 0.043* |
| CDTR-PI 400 mg vs CXM-AX | 0.293 |
| CDTR-PI 200 mg vs CDTR-PI 400 mg | 0.348 |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

n/N = number of pathogens eradicated/number of pathogens isolated pretreatment

* Statistical significance at the 0.05 level.

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

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.

**Clinical Reviewer's Note:** *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.*

**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, for both clinical trials. The 90 case report forms were submitted on April 24, 2000. The FDA analysis of these patient groups for this study was then compared to the applicant's results for these groups.
The results are shown in the following table.

Table 15. 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 | 23/28 (82.1%) | 23/28 (82.1%) |
| Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*) | 10/11 (90.9%) | 9/11 (81.8%) |
| Cefditoren 400 mg group | | |
| Clinical cure rate | 22/26 (84.6%) | 20/26 (76.9%) |
| Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*) | 6/8 (75.0%) | 6/8 (75.0%) |
| Cefuroxime 250 mg group | | |
| Clinical cure rate | 24/26 (92.3%) | 23/26 (88.5%) |
| Patient Microbiologic cure rate for target Pathogens (*S. aureus* and *S. pyogenes*) | 8/10 (80.0%) | 7/10 (70.0%) |

The clinical cure rates for the three blinded treatment groups as determined by the applicant 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's 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 seen by the FDA. Although the numbers are very small, the cure rate among the patients who had an infection caused by either *S. aureus* or *S. pyogenes* was also higher in the 200 mg group than the 400 mg group, 90.9% versus 75.0% and 81.8% versus 75.0%.

**Clinical Reviewer's Note:** *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 sponsor 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. Table 16 shows the results of the re-analysis along with the cure rates found in the initial submission. 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.

**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 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. 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 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 95% CIs for the differences as determined by the sponsor.*

**Microbiology**

Table 17 shows the results of the reanalysis 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 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.*

**Table 16. Re-analysis of Clinical and Patient Microbiological Data**

**Cef-97-009**

| 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 | 223/265 (84%) | 214/265 (81%) | 212/265 (80%) |
| Patient Micro. Cures | 110/135 (81%) | 104/135 (77%) | 103/135 (76%) |
| | | | |
| Cefditoren 400 mg group | | | |
| Clinical cures | 216/257 (84%) | 202/257 (79%) | 201/257 (78%) |
| Patient Micro. Cures | 121/143 (85%) | 114/143 (80%) | 113/143 (79%) |
| | | | |
| Cefuroxime 250 mg group | | | |
| Clinical cures | 234/265 (88%) | 225/265 (85%) | 223/265 (84%) |
| Patient Micro. Cures | 103/121 (85%) | 100/121 (83%) | 98/121 (81%) |

* Confidence intervals for differences in cure rates between groups

| | P-Values | 95% CI for difference |
|---|---|---|
| Clinical Response – Cures | | |
| Cefditoren 200mg vs Cefuroxime | 0.257 | [ -10.7, 2.4 ] |
| Cefditoren 400mg vs Cefuroxime | 0.093 | [ -12.6, 0.8 ] |
| Cefditoren 200mg vs Cefditoren 400mg | 0.667 | [ -5.2, 8.8 ] |
| Microbiological Response – Cures | | |
| Cefditoren 200mg vs Cefuroxime | 0.446 | [ -14.7, 5.3 ] |
| Cefditoren 400mg vs Cefuroxime | 0.759 | [ -11.6, 7.7 ] |
| Cefditoren 200mg vs Cefditoren 400mg | 0.666 | [ -12.5, 7.1 ] |

## Table 17. Re-analysis of the Pathogen Eradication Data

**Cef-97-009**

| 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* | 67/81 (83%) | 63/81 (78%) | 63/81 (78%) |
| *S. pyogenes* | 9/10 (90%) | 8/10 (80%) | 8/10 (80%) |
| | | | |
| Cefditoren 400 mg group | | | |
| *S. aureus* | 76/87 (87%) | 72/87 (83%) | 72/87 (83%) |
| *S. pyogenes* | 9/10 (90%) | 9/10 (90%) | 9/10 (90%) |
| | | | |
| Cefuroxime 250 mg group | | | |
| *S. aureus* | 59/67 (88%) | 57/67 (85%) | 55/67 (82%) |
| *S. pyogenes* | 6/6 (100%) | 5/6 (83%) | 5/6 (83%) |

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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=857) were included in the safety analyses.

**Adverse Events As Reported by the Applicant**

An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Patients were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken. The investigator assessed any adverse event and recorded all necessary information in detail onto the adverse event section of the CRF. The description of each adverse event included the date of onset and remission, severity, causal relationship to study drug, results of any diagnostic procedures or laboratory tests, all treatments that were required, and the outcome of the event. All patients experiencing adverse events were to be followed by the investigator until the adverse event returned to baseline or a clinically satisfactory resolution was achieved.

The investigator used the following definitions to rate the severity of the adverse event:

Mild -- The adverse event was transient and was easily tolerated by the patient.

Moderate -- The adverse event caused the patient discomfort and interrupted the patient's normal activities.

Severe -- The adverse event caused considerable interference with the patient's normal activities and may have been incapacitating or life-threatening.

The relationship of the adverse event to the study drug was assessed by the investigator using the following definitions:

Definite -- The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and satisfied any of the following:

Reappearance of similar reaction by repeated exposure (rechallenge);
Positive results in drug sensitivity tests (lymphocyte blastoid transformation test, skin test, etc.);
Toxic level of the drug in the blood or other body fluids.

Probable -- The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and the possibilities of factors other than the drug, such as underlying disease complications, concomitant drugs, or concurrent treatment, could be excluded.

Possible -- The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and the possibility of drug involvement could not be excluded, e.g., existence of similar reports attributable to the suspected drug, its analog or its pharmacological effect. However, other factors, such as underlying disease complications, concomitant drugs, or concurrent treatment, were presumable.

Not Related -- The adverse event did not follow a reasonable temporal sequence from administration of the drug or it could be reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.

Adverse events were listed with the investigator's original description and the COSTART medical term and body system classification. Adverse event incidence rates by COSTART term and body system were calculated and summarized by treatment group during treatment (from the first day of study drug to 3 days after the last dose of study drug) and posttreatment (at least 4 days after the last dose of study drug). The incidence rates were summarized separately for all adverse events and for those considered possibly, probably, or definitely study drug-related. Fisher's exact test was used to assess treatment group differences in adverse event incidence rates.

A patient with two or more adverse events with the same COSTART term was counted only once for that term. In addition, a patient who reported two or more different COSTART terms within the same body system was counted only once in the body system total, and a patient with two or more adverse events in different body systems was counted only once in the overall total.

Adverse events were summarized by severity and treatment group during treatment and posttreatment. The adverse events were summarized separately for all adverse events and for those considered possibly, probably, or definitely study drug-related. In the tabulations of adverse events by severity, patients who had more than one designation of severity for the same event were counted only once based on the most severe occurrence of that event; patients with multiple events of varying severity were counted only once in the overall total based on their most severe event.

Adverse events were also summarized by relationship to study drug and treatment group during treatment and posttreatment. In the tabulations of adverse events by relationship to study drug, patients with multiple events of varying relation to study drug were counted only once in the overall total based on their most related event, i.e., greatest degree of relationship to study drug.

Subgroup analyses of adverse event rates during treatment, adjusted for age, gender and race, were performed using Cochran-Mantel-Haenszel methodology.

**All Adverse Events**

Summaries of all adverse events grouped by body system and COSTART term occurring during treatment and during post-treatment are shown in the following tables. A summary of all adverse events during treatment reported by ≥2% of patients in any of the three treatment groups is shown in Table 18.

**Table 18. Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)**

| | CDTR-PI 200 mg BID (N=291) | | | | | CDTR-PI 400 mg BID (N=283) | | | | | CXM-AX 250 mg BID (N=283) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Severity[b] | | | | | Severity[b] | | | | | Severity[b] | | | | |
| Adverse Events | Mild | Mod | Sev | Total | % | Mild | Mod | Sev | Total | % | Mild | Mod | Sev | Total | % |
| OVERALL[c]† | | | | 96 | (33%) | | | | 128 | (45%) | | | | 99 | (35%) |
| BODY AS A WHOLE | | | | 35 | (12%) | | | | 41 | (14%) | | | | 36 | (13%) |
| Abdominal pain | 1 | 1 | 0 | 2 | ( 1%) | 2 | 4 | 1 | 7 | ( 2%) | 1 | 2 | 1 | 4 | ( 1%) |
| Asthenia | 2 | 1 | 0 | 3 | ( 1%) | 4 | 1 | 0 | 5 | ( 2%) | 0 | 0 | 0 | 0 | ( 0%) |
| Headache | 11 | 4 | 1 | 16 | ( 5%) | 4 | 5 | 2 | 11 | ( 4%) | 8 | 3 | 3 | 14 | ( 5%) |
| Infection | 2 | 2 | 0 | 4 | ( 1%) | 4 | 2 | 2 | 8 | ( 3%) | 2 | 2 | 0 | 4 | ( 1%) |
| DIGESTIVE SYSTEM[c]† | | | | 57 | (20%) | | | | 91 | (32%) | | | | 46 | (16%) |
| Diarrhea[c]†# | 26 | 9 | 3 | 38 | (13%) | 44 | 11 | 3 | 58 | (20%) | 13 | 4 | 2 | 19 | ( 7%) |
| Dyspepsia | 2 | 2 | 1 | 5 | ( 2%) | 2 | 2 | 1 | 5 | ( 2%) | 4 | 3 | 1 | 8 | ( 3%) |
| Flatulence[c] | 1 | 0 | 0 | 1 | (<1%) | 6 | 2 | 0 | 8 | ( 3%) | 2 | 0 | 0 | 2 | ( 1%) |
| Nausea[c]† | 11 | 2 | 1 | 14 | ( 5%) | 19 | 6 | 3 | 28 | (10%) | 6 | 7 | 0 | 13 | ( 5%) |
| Vomiting | 1 | 1 | 0 | 2 | ( 1%) | 6 | 1 | 1 | 8 | ( 3%) | 2 | 1 | 0 | 3 | ( 1%) |
| SKIN AND APPENDAGES | | | | 13 | ( 4%) | | | | 10 | ( 4%) | | | | 11 | ( 4%) |
| Pruritus | 4 | 2 | 1 | 7 | ( 2%) | 2 | 0 | 0 | 2 | ( 1%) | 1 | 2 | 0 | 3 | ( 1%) |
| UROGENITAL | | | | (N=138) | | | | | (N=142) | | | | | (N=151) | |
| SYSTEM (female)[d] | | | | 4 | ( 3%) | | | | 7 | ( 5%) | | | | 7 | ( 5%) |
| Vaginal Moniliasis[d] | 1 | 0 | 0 | 1 | ( 1%) | 3 | 2 | 0 | 5 | ( 4%) | 3 | 2 | 0 | 5 | ( 3%) |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; Mod = moderate; Sev = severe

[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.
[c] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CDTR-PI 400 mg groups ($p \leq 0.05$).
† Statistically significant difference in incidence rate between the CDTR-PI 400 mg and CXM-AX groups ($p \leq 0.05$).
# Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CXM-AX groups ($p \leq 0.05$).

Of the 857 randomized patients who received study drug, 96 patients (33%) in the 200 mg cefditoren group, 128 patients (45%) in the 400 mg cefditoren group, and 99 patients (35%) in the cefuroxime group reported at least one adverse event during treatment. According to the applicant, the differences in the incidence of adverse events were statistically significant between the two cefditoren groups (p=0.003) and between the 400 mg cefditoren group and cefuroxime group (p=0.016). The most commonly reported adverse events during treatment in all three treatment groups (200 mg cefditoren, 400 mg cefditoren, and cefuroxime) included diarrhea (13%, 20%, and 7%, respectively), nausea (5%, 10%, and 5%, respectively), and headache (5%, 4%, and 5%, respectively). As determined by the applicant, statistically significant differences were observed in the incidence of diarrhea between the two cefditoren groups (p=0.019) and between each cefditoren group and the cefuroxime group ($p \leq 0.012$); and in the incidence of nausea between the two cefditoren groups (p=0.024) and between the 400 mg cefditoren and cefuroxime groups (p=0.022).

**Treatment-Related Adverse Events**

The following table shows a summary of the treatment-related adverse events that were reported by ≥2% of patients in any treatment group.

**Table 19. Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)**

| | CDTR-PI 200 mg BID (N=291) | | | | | CDTR-PI 400 mg BID (N=283) | | | | | CXM-AX 250 mg BID (N=283) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Severity[b] | | | | | Severity[b] | | | | | Severity[b] | | | | |
| Adverse Events | Mild | Mod | Sev | Total | % | Mild | Mod | Sev | Total | % | Mild | Mod | Sev | Total | % |
| OVERALL[c@†] | | | | 64 | (22%) | | | | 94 | (33%) | | | | 64 | (23%) |
| BODY AS A WHOLE | | | | 15 | ( 5%) | | | | 22 | ( 8%) | | | | 13 | ( 5%) |
| Abdominal Pain | 1 | 1 | 0 | 2 | ( 1%) | 2 | 4 | 1 | 7 | ( 2%) | 1 | 2 | 0 | 3 | ( 1%) |
| Headache | 5 | 3 | 1 | 9 | ( 3%) | 3 | 5 | 1 | 9 | ( 3%) | 2 | 1 | 2 | 5 | ( 2%) |
| DIGESTIVE SYSTEM@† | | | | 51 | (18%) | | | | 79 | (28%) | | | | 42 | (15%) |
| Diarrhea†# | 25 | 9 | 3 | 37 | (13%) | 40 | 9 | 3 | 52 | (18%) | 13 | 4 | 2 | 19 | ( 7%) |
| Dyspepsia | 2 | 2 | 1 | 5 | ( 2%) | 2 | 2 | 1 | 5 | ( 2%) | 4 | 3 | 1 | 8 | ( 3%) |
| Flatulence@ | 1 | 0 | 0 | 0 | (<1%) | 6 | 2 | 0 | 8 | ( 3%) | 2 | 0 | 0 | 2 | ( 1%) |
| Nausea† | 11 | 1 | 1 | 13 | ( 4%) | 15 | 5 | 3 | 23 | ( 8%) | 3 | 7 | 0 | 10 | ( 4%) |
| SKIN AND APPENDAGES | | | | 6 | ( 2%) | | | | 2 | ( 1%) | | | | 4 | ( 1%) |
| Pruritus | 3 | 2 | 1 | 6 | ( 2%) | 1 | 0 | 0 | 1 | (<1%) | 0 | 1 | 0 | 1 | (<1%) |
| UROGENITAL SYSTEM (female)[d] | | | | (N=138) 2 | ( 1%) | | | | (N=142) 6 | ( 4%) | | | | (N=151) 6 | ( 4%) |
| Vaginal Moniliasis[d] | 1 | 0 | 0 | 1 | ( 1%) | 3 | 2 | 0 | 5 | ( 4%) | 3 | 2 | 0 | 5 | ( 3%) |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; Mod = moderate; Sev = severe

[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.
[@] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CDTR-PI 400 mg groups ($p \leq 0.05$).
[†] Statistically significant difference in incidence rate between the CDTR-PI 400 mg and CXM-AX groups ($p \leq 0.05$).
[#] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CXM-AX groups ($p \leq 0.05$).

Sixty-four (22%) patients in the 200 mg cefditoren group, 94 (33%) patients in the 400 mg cefditoren group, and 64 (23%) patients in the cefuroxime group reported at least one adverse event during treatment that was considered by the investigator to be possibly, probably, or definitely treatment-related . According to the applicant, the differences in the incidence of treatment-related adverse events were statistically significant between the two cefditoren groups (p=0.003) and between the 400 mg cefditoren and cefuroxime groups (p=0.006). The most frequently occurring treatment-related adverse events were diarrhea (13%) in the 200 mg cefditoren group; diarrhea (18%) and nausea (8%) in the 400 mg cefditoren group; and diarrhea (7%) in the cefuroxime group. As determined by the applicant, statistically significant differences were observed between the 200 mg cefditoren and cefuroxime groups (p=0.017) and between the 400 mg cefditoren and cefuroxime groups (p<0.001) in the incidence of diarrhea.

### Analysis of Adverse Events

The most common adverse events in all three treatment groups (200 mg cefditoren, 400 mg cefditoren, and cefuroxime were associated with the digestive system (20%, 32%, and 16%, respectively) and the body as a whole (12%, 14%, and 13%, respectively). According to the sponsor, statistically significant difference was observed between the two cefditoren groups (p=0.001) and between the 400 mg cefditoren and cefuroxime groups (p<0.001) in the incidence of adverse events associated with the digestive system. A summary of all adverse events grouped by body system is presented by treatment group in Table 20.

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**Table 20. Summary of All Adverse Events Grouped by Body System (During Treatment)**

| | Number (%) of Patients[a] | | | | | |
|---|---|---|---|---|---|---|
| | CDTR-PI 200 mg BID (N=291) | | CDTR-PI 400 mg BID (N=283) | | CXM-AX 250 mg BID (N=283) | |
| Body System | | | | | | |
| OVERALL[b@†] | 96 | (33%) | 128 | (45%) | 99 | (35%) |
| Body as a Whole | 35 | (12%) | 41 | (14%) | 36 | (13%) |
| Cardiovascular | 0 | ( 0%) | 1 | (<1%) | 1 | (<1%) |
| Digestive[@†] | 57 | (20%) | 91 | (32%) | 46 | (16%) |
| Hemic and Lymphatic | 0 | ( 0%) | 4 | ( 1%) | 2 | ( 1%) |
| Metabolic and Nutritional Disorders | 5 | ( 2%) | 2 | ( 1%) | 2 | ( 1%) |
| Musculoskeletal | 2 | ( 1%) | 3 | ( 1%) | 0 | ( 0%) |
| Nervous | 8 | ( 3%) | 13 | ( 5%) | 7 | ( 2%) |
| Respiratory | 8 | ( 3%) | 5 | ( 2%) | 5 | ( 2%) |
| Skin and Appendages | 13 | ( 4%) | 10 | ( 4%) | 11 | ( 4%) |
| Special Senses | 3 | ( 1%) | 1 | (<1%) | 6 | ( 2%) |
| Urogenital | 1 | (<1%) | 2 | ( 1%) | 3 | ( 1%) |
| Urogenital[c] (females) | 4 | ( 3%) | 7 | ( 5%) | 7 | ( 5%) |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

[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.

[@] Statistically significant difference ($p \leq 0.05$) between the CDTR-PI 200 mg and CDTR-PI 400 mg groups.

[†] Statistically significant difference ($p \leq 0.05$) between the CDTR-PI 400 mg and CXM-AX groups.

The most common treatment-related adverse events in all three treatment groups (200 mg cefditoren, 400 mg cefditoren, and cefuroxime were associated with the digestive system (18%, 28%, and 15%, respectively) and the body as a whole (5%, 8%, and 5%, respectively). As determined by the applicant, a statistically significant difference was observed between the two cefditoren groups ($p=0.004$) and between the 400 mg cefditoren and cefuroxime groups ($p<0.001$) in the incidence of adverse events associated with the digestive system. A summary of treatment-related adverse events grouped by body system is presented by treatment group in Table 21.

**Table 21. Summary of Treatment-Related Adverse Events Grouped by Body System (During Treatment)**

| | Number (%) of Patients[a] | | | | | |
|---|---|---|---|---|---|---|
| Body System | CDTR-PI 200 mg BID (N=291) | | CDTR-PI 400 mg BID (N=283) | | CXM-AX 250 mg BID (N=283) | |
| OVERALL[b@†] | 64 | (22%) | 94 | (33%) | 64 | (23%) |
| Body as a Whole | 15 | ( 5%) | 22 | ( 8%) | 13 | ( 5%) |
| Cardiovascular | 0 | ( 0%) | 1 | (<1%) | 0 | ( 0%) |
| Digestive[@†] | 51 | (18%) | 79 | (28%) | 42 | (15%) |
| Hemic and Lymphatic | 0 | ( 0%) | 0 | ( 0%) | 1 | (<1%) |
| Musculoskeletal | 0 | ( 0%) | 1 | (<1%) | 0 | ( 0%) |
| Metabolic and Nutritional Disorders | 1 | (<1%) | 0 | ( 0%) | 2 | ( 1%) |
| Nervous | 3 | ( 1%) | 8 | ( 3%) | 4 | ( 1%) |
| Respiratory | 1 | (<1%) | 1 | (<1%) | 0 | ( 0%) |
| Skin and Appendages | 6 | ( 2%) | 2 | ( 1%) | 4 | ( 1%) |
| Special Senses | 1 | (<1%) | 0 | ( 0%) | 4 | ( 1%) |
| Urogenital | 0 | ( 0%) | 1 | (<1%) | 1 | (<1%) |
| Urogenital[c] (females) | 2 | ( 1%) | 6 | ( 4%) | 6 | ( 4%) |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

[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.

[@] Statistically significant difference ($p \leq 0.05$) between the CDTR-PI 200 mg and CDTR-PI 400 mg groups.

[†] Statistically significant difference ($p \leq 0.05$) between the CDTR-PI 400 mg and CXM-AX groups.

**Serious Adverse Events:** A serious adverse event was defined as any drug experience, at any dose, that resulted in any of the following outcomes:

- Death;
- Life-threatening (patient was at risk of death at the time the event occurred);
- Inpatient hospitalization (>23 hours) or prolongation of existing hospitalization;
- Congenital anomaly or birth defect;
- Persistent or significant disability or incapacity.

In addition, other important medical events may have been considered serious when based upon appropriate medical judgment, they jeopardized the patient and required medical or surgical intervention to prevent one of the previously listed serious adverse event outcomes. In the case of a serious adverse event, the sites were instructed to contact the sponsor or designee within 24 hours with subsequent notification to the IRB.

**Table 22. 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** | | | | | | |
| Faircloth 7001 | 41/M | 21 (11) | 23 (13) | Body as a Whole | Cellulitis | Required Intervention |
| | | 24 (14) | 67 (57) | Musculoskeletal | Osteomyelitis | Required Intervention |
| Larsen S 7253# | 67/M | 11 ( 7) | Cont.: 95 (91) | Nervous | Cerebrovascular accident | Hospitalization Life-Threatening |
| **Patients with Serious Adverse Events in the Cefditoren Pivoxil 400 mg BID Treatment Group** | | | | | | |
| Garrison 7267# | 58/M | 2 ( 1) | 6 (5) | Body as a Whole | Infection | Hospitalization |
| Muluk 7361# | 64/M | 5 ( 1) | Cont.: 6 (2) | Digestive | Gastrointestinal hemorrhage | Hospitalization |
| Williams C. 7788# | 31/M | 3 ( 0) | Cont.: 33 (30) | Body as a Whole | Infection | Hospitalization |
| **Patients with Serious Adverse Events in the Cefuroxime Axetil 250 mg BID Treatment Group** | | | | | | |
| Russell 7153 | 54/F | 17 ( 7) | 20 (10) | Body as a Whole | Infection | Hospitalization |
| Taylor 7638 | 70/F | 22 (12) | 32 (22) | Skin and Appendages | Skin ulcer | Hospitalization |

SAE = serious adverse event

\# Patient prematurely discontinued from the study.

[a] Days posttreatment are presented in parentheses; (0) = study drug discontinued as of specified day; Cont. = event continued as of specified day.

**Clinical Reviewer's Note:** *There were two patients in the 200 mg cefditoren group, three patients in the 400 mg cefditoren group, and two patients in the cefuroxime 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 23 is a summary of treatment discontinuations due to adverse reactions. It shows that 10 patients in the 200 mg cefditoren group, 16 patients in the 400 mg cefditoren group, and only five patients in the cefuroxime group discontinued the study due to adverse events.

**Clinical Reviewer's Note:** *The high number of patient discontinuations due to adverse events in the 400 mg cefditoren group (16) compared to the number in the cefuroxime group (5) may be significant. There also were twice as many discontinuations in the 200 mg cefditoren group compared to the control drug. These differences are most likely due to the incidence of digestive adverse events, especially diarrhea, in cefditoren treated patients.*

**Table 23. 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** | | | | | |
| Casale 7142 | 60/F | 4 (0) | 9 (5) | Digestive | Diarrhea[b] |
| Coalson 7918 | 59/F | 7 | 40 (31) | Digestive | Diarrhea[b] |
| Gezon 7881 | 81/M | 1 | 3 (1) | Digestive | Nausea and vomiting[b] |
| Goffe 7367 | 27/M | 1 | 8 (1) | Body as a Whole | Abdominal pain[b] |
| | | 1 | 8 (1) | Digestive | Nausea[b] |
| | | 1 | 8 (1) | Digestive | Vomiting[b] |
| Larsen S 7253 | 67/M | 11 (7) | 95 (91) | Nervous | Cerebrovascular accident |
| Markunas 7685 | 20/F | 5 | Cont.: 9 (3) | Skin and Appendages | Rash |
| Resnick 7894 | 23/M | 1 | 4 (1) | Skin and Appendages | Pruritus[b] |
| | | 1 | 4 (1) | Skin and Appendages | Rash[b] |
| Sievers 7666 | 38/F | 4 (0) | 5 (1) | Body as a Whole | Headache[b] |
| Williams C. 8070 | 65/F | 7 | 106 (95) | Digestive | Diarrhea[b] |
| Yeoman 7203 | 56/M | 5 | 6 (0) | Body as a Whole | Headache[b] |
| **Patients Discontinued from the Cefditoren Pivoxil 400 mg BID Treatment Group** | | | | | |
| Alwine 7045 | 45/F | 1 | 2 (0) | Digestive | Nausea[b] |
| Alwine 7284 | 34/M | 2 | 8 (4) | Digestive | Diarrhea[b] |
| | | 2 | 13 (9) | Body as a Whole | Abdominal pain[b] |
| Asher 7250 | 23/M | 3 | 8 (1) | Digestive | Nausea[b] |
| Coalson 7917 | 30/F | 3 | 12 (1) | Digestive | Diarrhea[b] |
| Drehobl 7608 | 48/M | 2 (0) | 3 (1) | Body as a Whole | Asthenia[b] |
| | | 3 (1) | [10 minutes] | Digestive | Diarrhea[b] |
| | | 3 (1) | [2 hours] | Digestive | Nausea[b] |
| Faust 7463 | 29/F | 2 (1) | 9 (8) | Body as a Whole | Allergic reaction[b] |
| Faust 7941 | 81/F | 2 | 3 (0) | Digestive | Flatulence[b] |
| | | 2 | 3 (0) | Cardiovascular | Tachycardia[b] |
| Garrison 7267 | 58/M | 2 (1) | 6 (5) | Body as a Whole | Infection |
| Garrison 7513 | 69/F | 2 | 7 (4) | Digestive | Flatulence[b] |
| | | 2 | 7 (4) | Digestive | Diarrhea[b] |
| Gezon 7878 | 32/F | 2 | 12 (3) | Digestive | Nausea[b] |
| | | 2 | 12 (3) | Skin and Appendages | Pruritus[b] |
| | | 2 | 12 (3) | Digestive | Vomiting[b] |
| Green 7960 | 43/M | 2 | 8 (0) | Digestive | Diarrhea[b] |
| Maggiacomo 7077 | 71/F | 1 | Cont.: 3 (1) | Digestive | Diarrhea[b] |
| | | 1 | Cont.: 3 (1) | Digestive | Dyspepsia[b] |
| Markunas 7318 | 76/F | 3 | 4 (0) | Digestive | Vomiting |
| Muluk 7361 | 64/M | 5 (1) | Cont.: 6 (2) | Digestive | Gastrointestinal hemorrhage |
| Williams C. 7788 | 31/M | 3 (0) | Cont.: 33 (30) | Body as a Whole | Infection |
| Williams C. 7992 | 48/M | 4 | 5 (0) | Body as a Whole | Fever |
| | | 5 (0) | Cont.: 5 (0) | Special Senses | Otitis media |

Note: Study drug was prematurely discontinued for two additional patients, McAdoo 7175 and Williams C. 7590 in the CXM-AX group (listed in Appendix 16.2.7.4), who were classified as discontinuing primarily due to therapeutic failure and withdrawal of consent, respectively, with adverse event as a secondary reason.

[a] Days posttreatment are presented in parentheses; if less than 1 day, duration is presented in brackets; (0) = study drug discontinued as of specified day; Cont. = event continued as of specified day.

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

**Table 23. Patients Who Prematurely Discontinued Treatment Due to Adverse Events (continued)**

| Investigator Patient Number | Age/Sex | Day of Onset[a] | Day of Resolution[a] | Body System | COSTART Term |
|---|---|---|---|---|---|
| **Patients Discontinued from the Cefuroxime Axetil 250 mg BID Treatment Group** | | | | | |
| Green 7955 | 92/F | 4 (0) | 5 (1) | Digestive | Diarrhea[b] |
| Resnick 7845 | 24/M | 2 | Cont.: 3 | Digestive | Nausea[b] |
| Tucker 7804 | 20/F | 4 | Cont.: 20 (14) | Nervous | Dizziness[b] |
| | | 5 | 11 (5) | Digestive | Nausea[b] |
| | | 6 (0) | [2 hrs] | Body as a Whole | Chest pain[b] |
| Williams C. 7989 | 32/M | 6 (0) | 14 (8) | Digestive | Dyspepsia[b] |
| Yeoman 7451 | 50/F | 2 (0) | 3 (1) | Body as a Whole | Headache[b] |

Note: Study drug was prematurely discontinued for two additional patients, McAdoo 7175 and Williams C. 7590 in the CXM-AX group (listed in Appendix 16.2.7.4), who were classified as discontinuing primarily due to therapeutic failure and withdrawal of consent, respectively, with adverse event as a secondary reason.

[a] Days posttreatment are presented in parentheses; if less than 1 day, duration is presented in brackets; (0) = study drug discontinued as of specified day; Cont. = event continued as of specified day.

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

## Clinical Laboratory Values:

Laboratory tests were performed pretreatment, at the On-Therapy Visit, if scheduled during the telephone contact, and at the Post-Therapy Visit. Any clinically significant abnormal observations arising during the treatment period were followed to a satisfactory resolution. All blood and urine samples were collected and handled in accordance with accepted laboratory procedures. Specimens were obtained for the following tests.

**Table 24. Laboratory Tests**

| Hematology | | Serum Chemistry | |
|---|---|---|---|
| Hemoglobin | | Blood Urea Nitrogen (BUN) | Creatinine |
| Hematocrit | | Alkaline Phosphatase | Glucose |
| White Blood Cell Count (WBC) with Differential | | Inorganic Phosphorus | Calcium |
| Platelet Count | | Total Bilirubin | Albumin |
| **Urinalysis** | | Total Protein | Sodium |
| Specific Gravity | Urine pH | Lactic Dehydrogenase (LDH) | Cholesterol |
| Glucose | Albumin (protein) | Gamma Glutamyl Transferase (GGT) | Potassium |
| Hemoglobin | Microscopic examination | Aspartate aminotransferase (AST) | Chloride |
| | | Alanine aminotransferase (ALT) | |

Liver and renal function test(s) were to be repeated if one or more of the following was observed:

- AST > 2 X the upper limit of normal;
- ALT > 2 X the upper limit of normal;
- Alkaline phosphatase > 1.25 X the upper limit of normal;

- Creatinine > 2.0 mg/dL (if, in the investigator's opinion, the creatinine was elevated due to pretreatment dehydration, the serum creatinine could be repeated after rehydration of the patient);
- Blood urea nitrogen ≥ 30 mg/dL;
- Total bilirubin > 2 X the upper limit of normal (total bilirubin was to be repeated and a direct bilirubin was also to be performed).

A urine hCG pregnancy test was performed pretreatment on all females of childbearing potential. The test was to be negative for the patient to be enrolled.
An Abbott urine and/or serum hCG pregnancy test was provided with the clinical laboratory supplies, but other test kits could have been used at the discretion of the investigator.

Mean values at baseline and post-therapy were recorded, and mean change from baseline to post-therapy in clinical laboratory test variables were determined. Statistically significant treatment differences were observed among the treatment groups in mean change from baseline to post-therapy in ALT, albumin, calcium, and cholesterol. 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. A summary of the laboratory parameters for which statistically significant differences among and/or between treatment groups were observed in mean change from baseline to post-therapy is presented in Table 25.

**Table 25. Statistically Significant Differences in Mean Change From Baseline to Post-Therapy in Laboratory Test Parameters**

| Laboratory Parameter (unit) | CDTR-PI 200 mg BID N | CDTR-PI 200 mg BID Mean (SD) | CDTR-PI 400 mg BID N | CDTR-PI 400 mg BID Mean (SD) | CXM-AX 250 mg BID N | CXM-AX 250 mg BID Mean (SD) |
|---|---|---|---|---|---|---|
| **Lymphocytes (%)** | | | | | | |
| Baseline | 285 | 27.70 (8.68) | 270 | 27.65 (8.68) | 275 | 28.57 (9.13) |
| Post-Therapy | 252 | 30.12 (8.19) | 245 | 31.16 (8.67) | 249 | 31.32 (8.30) |
| Mean Change to Post-Therapy[@] | 246 | 2.12 (7.85) | 237 | 3.47 (7.19) | 242 | 2.59 (7.39) |
| **Sodium (mEq/dL)** | | | | | | |
| Baseline | 290 | 139.33 (2.76) | 279 | 139.30 (2.54) | 281 | 139.61 (2.29) |
| Post-Therapy | 258 | 139.17 (2.52) | 250 | 139.65 (2.33) | 253 | 139.76 (2.46) |
| Mean Change to Post-Therapy[@] | 257 | -0.24 (2.78) | 248 | 0.26 (2.69) | 251 | 0.10 (2.79) |
| **Potassium (mEq/dL)** | | | | | | |
| Baseline | 284 | 4.20 (0.41) | 273 | 4.20 (0.33) | 278 | 4.17 (0.37) |
| Post-Therapy | 257 | 4.14 (0.37) | 248 | 4.21 (0.37) | 252 | 4.17 (0.38) |
| Mean Change to Post-Therapy[@] | 251 | -0.06 (0.40) | 241 | 0.01 (0.38) | 247 | -0.01 (0.37) |
| **ALT (U/L)** | | | | | | |
| Baseline | 287 | 25.07 (19.72) | 276 | 24.20 (17.15) | 276 | 26.04 (19.68) |
| Post-Therapy | 256 | 26.29 (19.12) | 245 | 26.91 (19.79) | 252 | 26.38 (17.89) |
| Mean Change to Post-Therapy[*#] | 252 | 2.06 (9.82) | 242 | 3.05 (9.74) | 246 | 0.71 (11.88) |
| **Albumin (g/dL)** | | | | | | |
| Baseline | 287 | 4.10 (0.33) | 276 | 4.10 (0.37) | 276 | 4.10 (0.36) |
| Post-Therapy | 256 | 4.06 (0.33) | 245 | 4.11 (0.34) | 252 | 4.03 (0.35) |
| Mean Change to Post-Therapy[*@#] | 252 | -0.05 (0.27) | 242 | 0.02 (0.25) | 246 | -0.07 (0.25) |
| **Calcium (mg/dL)** | | | | | | |
| Baseline | 290 | 9.36 (0.40) | 279 | 9.40 (0.41) | 281 | 9.38 (0.38) |
| Post-Therapy | 258 | 9.31 (0.39) | 250 | 9.42 (0.38) | 253 | 9.29 (0.35) |
| Mean Change to Post-Therapy[*@#] | 257 | -0.06 (0.39) | 248 | 0.01 (0.41) | 251 | -0.09 (0.37) |
| **Cholesterol (mg/dL)** | | | | | | |
| Baseline | 290 | 190.06 (43.25) | 279 | 191.67 (41.80) | 281 | 190.03 (42.44) |
| Post-Therapy | 258 | 189.25 (39.38) | 250 | 188.90 (38.11) | 253 | 192.82 (40.79) |
| Mean Change to Post-Therapy[*S#] | 257 | -3.49 (22.45) | 248 | -3.65 (20.78) | 251 | 1.02 (18.76) |
| **Inorganic phosphorus (mg/dL)** | | | | | | |
| Baseline | 284 | 3.47 (0.56) | 273 | 3.51 (0.52) | 278 | 3.59 (0.57) |
| Post-Therapy | 257 | 3.50 (0.60) | 248 | 3.61 (0.62) | 252 | 3.56 (0.54) |
| Mean Change to Post-Therapy[#] | 251 | 0.03 (0.63) | 241 | 0.10 (0.59) | 247 | -0.01 (0.59) |
| **Urine pH** | | | | | | |
| Baseline | 279 | 5.76 (0.74) | 264 | 5.72 (0.77) | 271 | 5.67 (0.70) |
| Post-Therapy | 246 | 5.67 (0.71) | 234 | 5.79 (0.82) | 243 | 5.71 (0.72) |
| Mean Change to Post-Therapy[@] | 237 | -0.11 (0.93) | 225 | 0.07 (1.00) | 234 | 0.04 (0.94) |

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; SD = standard deviation
[*] = Statistically significant overall difference among treatment groups.
[@] = Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg.
[S] = Statistically significant difference between CDTR-PI 200 mg and CXM-AX.
[#] = Statistically significant difference between CDTR-PI 400 mg and CXM-AX.

**Deaths:** There were no deaths reported during the study.