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50-588

AE Letter

[illegible]

[illegible]

Please refer to your Antibiotic Form 5 dated January 20, 1984, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for [illegible] for Injection.

We have also received your additional [illegible] questions dated January 31, [illegible] 28, [illegible] and 16, July 27, [illegible] January 23, March 1, April [illegible], June [illegible] August [illegible] and 27, 1985.

We have completed our review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, prior to approval, you must submit twelve copies of the final printed labeling that incorporate the following changes in the labeling submitted August [illegible], 1985:

1. Under CLINICAL PHARMACOLOGY, the [illegible] paragraph after the tabular data should be worded as follows:

   > Active metabolites of cefotetan have been detected; however, small amounts (less than 7%) of cefotetan in plasma and urine may be converted to the tautomer, which has antimicrobial activity similar to [illegible].

2. [illegible] Urinary Tract Infections caused by E. coli, Klebsiella species (including K. pneumoniae), Proteus mirabilis and Proteus spp. (which may include the organisms now called Proteus vulgaris, Providencia rettgeri, and Morganella morganii).

3. An asterisk (*) should follow these bacteria under "INDICATIONS AND USAGE": "Gynecologic Infections" section, Staphylococcus aureus, "Intra-abdominal Infections" section, K. pneumoniae, and "Bone and Joint Infections" section, Staphylococcus aureus.

4. The statement "Efficacy for this organism in this organ system was studied in less than ten infections." should be changed to "Efficacy for this organism in this organ system was studied in fewer than ten infections."

5. Under "Carcinogenesis, Mutagenesis, Impairment of Fertility," the second paragraph should be revised to read:

[illegible] effects [illegible] of pregnancy [illegible] quantitation of [illegible] suppression [illegible] the fetal [illegible] rabbits on days [illegible] to assess [illegible] postnatal [illegible] late [illegible] in humans [illegible] to [illegible] weight [illegible] [illegible] degree [illegible] to [illegible] Effects [illegible] [illegible] unaffected. [illegible] and severity of lesions were [illegible] dependent; at 120 mg/kg/day [illegible], [illegible] the usual number [illegible] only 1 of 10 treated animals was affected, and the degree of [illegible] was mild. Similar lesions have been observed in experimental [illegible] comparable design [illegible] saline, [illegible] and [illegible] fluid-containing [illegible] and [illegible] have not been reported, particularly at [illegible] dose levels. No particular effects were observed in [illegible] rats treated with up to 1000 mg/kg/day IV for 5 weeks, or [illegible] of dogs (3 weeks) that received up to 200 mg/kg/day IV for 2 weeks. The relevance of these findings to humans is unknown."

6. The first sentence under the "Prophylaxis" subsection of DOSAGE AND ADMINISTRATION should be worded as follows:

> To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN (cefotetan disodium, sterile) [illegible] intravenously, 30 to 90 minutes prior to surgery.

If additional information relating to the safety or effectiveness of this drug becomes available, [illegible] the final printed labeling is submitted [illegible], further revision to the labeling may be necessary.

In addition, [illegible] you are required to update [illegible] certified copy of [illegible] to this [illegible] additional or investigational [illegible]. [illegible] to the Division of Drug [illegible] a copy of the [illegible] report.

[illegible] you must comply with the requirements set forth under CFR [illegible] and also [illegible] approved NDA [illegible] application.

NDA

50-588

FPL

PROFESSIONAL INFORMATION BROCHURE

CEFOTAN™

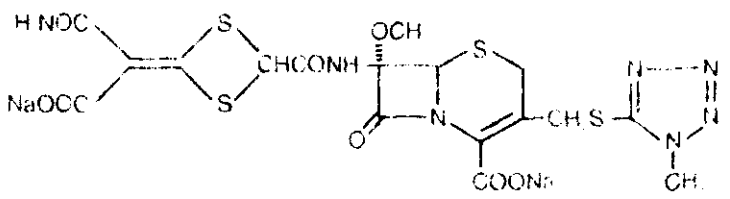
(cefotetan disodium)

For Intravenous or Intramuscular Use

DESCRIPTION

CEFOTAN™ (cefotetan disodium) is a sterile, semisynthetic, broad-spectrum beta-lactamase resistant cephalosporin (cephamycin) antibiotic for parenteral administration. It is the disodium salt of [6*R*, 7*S*(*Z*)]-7-[[[4-(diamino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular formula is $C_{17}H_{15}N_9Na_2O_8S_4$, with a molecular weight of 619.56.

STRUCTURAL FORMULA



CEFOTAN™ contains approximately 80 mg (2.5 mEq) of sodium per gram of cefotetan activity. It is a white to pale yellow powder which is very soluble in water. The solution varies from colorless to yellow depending on the concentration. The pH of freshly reconstituted solutions is usually between 4.5 to 6.5.

CLINICAL PHARMACOLOGY

High plasma levels of cefotetan are attained after intravenous and intramuscular administration of single doses to normal volunteers.

PLASMA CONCENTRATIONS AFTER 1.0 GRAM IV* or IM DOSE
Mean Plasma Concentration (µg/mL)

	Time After Injection						
Route	**15 min**	**30 min**	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**
IV	92	158	103	72	42	18	9
IM	34	56	71	68	47	20	9

*30-minute infusion

PLASMA CONCENTRATIONS AFTER 2.0 GRAM IV* or IM DOSE
Mean Plasma Concentration (µg/mL)

	Time After Injection						
Route	**5 min**	**10 min**	**1 h**	**3 h**	**5 h**	**9 h**	**12 h**
IV	237	223	135	74	48	22	12**
IM	–	20	75	91	69	33	19

*Injected over 3 minutes
**Concentrations estimated from regression line

The plasma elimination half-life of cefotetan is 3 to 4.6 hours after either intravenous or intramuscular administration.

Repeated administration of CEFOTAN™ (cefotetan disodium) does not result in accumulation of the drug in normal subjects.

Cefotetan is 88% plasma protein bound.

No active metabolites of cefotetan have been detected; however, small amounts (less than 7%) of cefotetan in plasma and urine may be converted to its tautomer which has antimicrobial activity similar to the parent drug.

In normal patients, from 51% to 81% of an administered dose of CEFOTAN™ is excreted unchanged by the kidneys over a 24 hour period which results in high and prolonged urinary concentrations. Following intravenous doses of 1 gram and 2 grams, urinary concentrations are highest during the first hour at peak concentrations of approximately 1700 and 3500 µg/mL respectively. In patients with reduced renal function, the plasma half-life of cefotetan is prolonged.

Therapeutic levels of cefotetan can be achieved in many body tissues and fluids including:

bile	endometrium	ureter	bile
muscle	cervix	bladder	peritoneal fluid
fat	ovary	maxillary sinus mucosa	umbilical cord serum
myometrium	kidney	tonsil	amniotic fluid

MICROBIOLOGY

The bactericidal action of cefotetan results from inhibition of cell wall synthesis. Cefotetan has in vitro activity against a wide range of gram-positive and gram-negative organisms. The methoxy group in the 7-alpha position provides cefotetan with a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases of gram-negative bacteria. Cefotetan is usually active against the following organisms in vitro and in clinical infections:

GRAM-NEGATIVE:

Escherichia coli
Klebsiella species (including *K pneumoniae*)
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Proteus mirabilis
Proteus vulgaris
Morganella morganii (formerly *Proteus morganii*)
Providencia rettgeri (formerly *Proteus rettgeri*)
Providencia stuartii
Haemophilus influenzae (including ampicillin-resistant strains)
Neisseria gonorrhoeae

NOTE: Approximately one-half of the strains of *Enterobacter* species, and *Citrobacter* species are resistant to cefotetan. Most strains of *Pseudomonas aeruginosa* and *Acinetobacter* species are resistant to cefotetan.

GRAM-POSITIVE:

Staphylococcus aureus (including penicillinase- and nonpenicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pyogenes (group A beta-hemolytic streptococci)
Streptococcus agalactiae (group B beta-hemolytic streptococci)
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins. Some strains of *Staphylococcus epidermidis* and most strains of enterococci, e.g., *S faecalis*, are resistant to cefotetan.

ANAEROBES:

Bacteroides fragilis subsp *fragilis*
Bacteroides bivius
Bacteroides distasonis
Bacteroides melaninogenicus
Bacteroides vulgatus
Fusobacterium species
Gram-positive bacilli (including *Clostridium* species)
Peptococcus and *Peptostreptococcus* species

NOTE: Most strains of *B distasonis*, *B ovatus* and *B thetaiotaomicron* are resistant to cefotetan.

Cefotetan also demonstrates in vitro activity against the following microorganisms, although its clinical significance is unknown: *Citrobacter* species (including *C diversus* and *C freundii*), *Serratia* species (including *S marcescens*), *Salmonella* species, *Shigella* species, *Yersinia enterocolitica*, *Clostridium difficile*, *B asaccharolyticus*, *B oralis*, *B splanchnicus*, *Veillonella* species, and *Propionibacterium* species.

NOTE: Many strains of *C difficile* are resistant.

SUSCEPTIBILITY TESTS

Diffusion Technique: Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with disks to test susceptibility to cefotetan. Organisms should be tested with the cefotetan 30 µg disk since cefotetan has been shown to be active in vitro against organisms which were found to be resistant to other beta-lactam antibiotics.

Reports from the laboratory with results of standardized single-disk susceptibility tests with a 30 µg cefotetan disk should be interpreted according to the following criteria.

Susceptible organisms produce zone sizes of 16 mm or greater, indicating that the tested organism is likely to respond to therapy.

Moderately susceptible organisms produce zones of 13 to 15 mm, indicating the test organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 12 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 µg cefotetan disk should give zone diameters between 17 and 22 mm for *S aureus* ATCC 25923. For *E coli* ATCC 25922, the zone diameters should be between 29 and 34 mm.

Dilution Techniques: Broth or agar dilution methods, e.g., ICS agar dilution[2] or an equivalent method such as that recommended by the National Committee for Clinical Laboratory Standards (NCCLS)[3], may be used to determine the minimal inhibitory concentration (MIC) of cefotetan.

Organisms inhibited by cefotetan at 16 µg/mL or less are considered susceptible. Organisms with MIC values 64 µg/mL or more are considered resistant to cefotetan.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefotetan powder should give MIC values in the range of 4 µg/mL and 16 µg/mL for *S aureus* ATCC 25923. For *E coli* ATCC 25922, the MIC range should be between 0.06 µg/mL and 0.25 µg/mL.

INDICATIONS AND USAGE

TREATMENT

CEFOTAN™ (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary Tract Infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus spp* (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and Skin Structure Infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic Infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species*, and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

Intra-abdominal Infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and Joint Infections caused by *Staphylococcus aureus**.

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN™ concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN™ and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN™ was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN™ is used concomitantly with an aminoglycoside.

PROPHYLAXIS

The preoperative administration of CEFOTAN™ may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as clean-contaminated or potentially contaminated (e.g., cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN™ should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN™ should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN™ (cefotetan disodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

(CONTINUED ON REVERSE SIDE)

WARNINGS

Before therapy with CEFOTAN™ is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN™ occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes should also be considered.

PRECAUTIONS

General: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN™ may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN™ may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN™ should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN™ administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN™.

Drug Interactions: Although to date nephrotoxicity has not been noted when CEFOTAN™ was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN™ is used concomitantly with an aminoglycoside.

Drug/Laboratory Test Interactions: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx. 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and pre-puberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 20 mg/kg/day (approx. 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7 week old rats treated with up to 1000 mg/kg/day SC for 5 weeks or in adult dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

Usage in Pregnancy. Pregnancy Category B. Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Usage in Nursing Mothers: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN™ (cefotetan disodium) therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients, the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive Direct Coombs test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT

The usual adult dosage is 1 or 2 grams of CEFOTAN™ administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN™

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults: The recommended dosage is 1 or 2 g of CEFOTAN® (cefotetan disodium) administered once intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION

When renal function is impaired a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.9 X value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

PREPARATION OF SOLUTION

For Intravenous Use: Reconstitute with Sterile Water for Injection. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent To Be Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	10	10.4	97.2
2 gram	10-20	11.0-21.0	179.8-98.4

Infusion bottles (100 mL) may be reconstituted with 50 to 100 mL of 5% Dextrose Solution or 0.9% Sodium Chloride Solution.

For Intramuscular Use: Reconstitute with Sterile Water for Injection, Bacteriostatic Water for Injection, Normal Saline, USP; 0.5% Lidocaine HCl; or 1.0% Lidocaine HCl. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent To Be Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	2	2.4	375.0
2 gram	3	3.9	471.5

INTRAVENOUS ADMINISTRATION

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent intravenous administration, a solution containing 1 gram or 2 grams of CEFOTAN® in Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, the solution may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN®, it is advisable to discontinue temporarily the administration of other solutions at the same site.

NOTE: Solutions of CEFOTAN® must not be admixed with solutions containing aminoglycosides. If CEFOTAN® and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.

INTRAMUSCULAR ADMINISTRATION

As with all intramuscular preparations, CEFOTAN® should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

COMPATABILITY AND STABILITY

CEFOTAN® reconstituted as described above (Preparation of Solution) maintains satisfactory potency for 24 hours at room temperature (25°C), for 96 hours under refrigeration (5°C), and for at least 1 week in the frozen state. After reconstitution and subsequent storage in disposable glass or plastic syringes, CEFOTAN® is stable for 24 hours at room temperature and 96 hours under refrigeration.

Frozen samples should be thawed at room temperature before use. After the periods mentioned above, any unused solutions or frozen materials should be discarded. Do not refreeze.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

CEFOTAN® (cefotetan disodium) is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10)
2 g in 20 mL vial (NDC 0038-0377-20)
1 g in 100 mL vial (NDC 0038-0376-11)
2 g in 100 mL vial (NDC 0038-0377-21)

1. Am J Clin Pathol 1966;45:493
Federal Register 1974;39:19182-19184.
2. Ericson HM, Sherris JC: Acta Pathol Microbiol Immunol Scand (B) 1971, (suppl No. 217).
3. Thornsberry C, et al: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 1983, Vol 3, No. 2.

Manufactured For
STUART PHARMACEUTICALS | Div. of ICI Americas Inc.
WILMINGTON, DELAWARE 19897

Rev. D 1/86

63967-01

NDA

50588

MOR

Original submission of 131 volumed dated: January 20, 1984
Received by reviewer: May 29, 1984

Amendment for prophylaxis 56 volumes dated: April 9, 1985
Received by reviewer: April 11, 1985

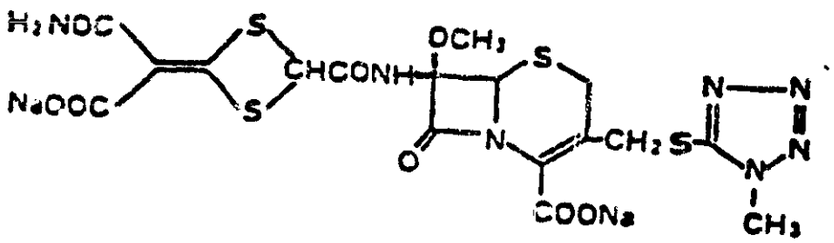
Review completed: May 23, 1985

Sponsor: Stuart Pharmaceuticals
Division of ICI Americas Inc.
Wilmington, Delaware 19897

Drug Name: Trade: Apacef
Generic: cefotetan disodium for injection
Chemical: Cefotetan is the disodium salt of

[6R-(6α,7α)]-7-[[[4-(2-amino-2-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular formula is $C_{17}H_{15}N_7Na_2O_8S_4$ with a molecular weight of 619.56.

Structural Formula:



PACKAGED 6/8/85
Rec'd by HFN-235 on
2/12/86 R.S.

fficer's Review and Evaluation of Clinical Data (MOR #1)

l submission of 131 volumed dated: January 20, 1984
Received by reviewer: May 29, 1984

Pharmacology Category: Cefotetan is a semisynthetic broad spectrum, beta-lactamase resistant, cephalosporin antibiotic for parenteral administration. It is 88% plasma protein bound and has a half-life of approximately 3 to 4.6 hours which makes once or twice a day dosing possible for some indications.

Proposed Indications: The sponsor submits data intended to support the use of cefotetan in the treatment of infections of the urinary tract, lower respiratory tract, skin and skin-structures, female genital tract, abdominal cavity, and bone and joint structures caused by a wide variety of susceptible gram-positive and gram-negative organisms, and Bacteroides fragilis, as well as surgical prophylaxis.

Background:

Cefotetan (APACEF) was synthesized in the Research Laboratories of Yamonouchi Pharmaceutical Company, Tokyo, Japan in 1976. Preclinical studies began in Japan in 1977, followed by clinical studies in 1979. An application for approval of the drug was submitted to the Japanese regulatory authority by Yamanouchi in 1982 and production approval has been granted. Outside of Japan, the drug is being developed by Imperial Chemical Industries PLC (ICI) in Europe and by Stuart Pharmaceuticals, a division of ICI Americas., in the United States. Clinical studies in Europe and the United States began late in 1981. In the United Kingdom, a product license application was submitted to the CSM in August of 1983. More than 4000 patients had been treated in cefotetan clinical trials world-wide at the time of submission of the application.

Included in this application were six pivotal clinical pharmacology studies, two conducted in the United States and four in the United Kingdom; summary reports from 18 other pharmacology studies conducted outside the United States, mostly in Japan; as well as 23 published papers that provide supportive clinical pharmacology information.

The effectiveness and safety of cefotetan were evaluated in seven controlled and two uncontrolled multicenter clinical trials conducted throughout the United States. Eighteen hundred and ten patients were enrolled in these studies, including 1,451 patients treated with cefotetan and 359 treated with comparative drugs: cefoxitin, moxalactam, and cefotaxime.

In addition, the results of 6 United States, multicenter, comparative studies of the use of cefotetan in surgical prophylaxis were submitted involving 399 evaluable patients given cefotetan and 273 given a comparative antibiotic.

Index

I. Clinical Pharmacology

A. Conclusions reached from review of clinical pharmacology data.

1. High plasma levels of cefotetan were attained after intravenous and intramuscular administration of single doses of cefotetan to normal subjects. The plasma levels declined slowly with a mean half-life ranging between 3 and 4.6 hours. The plasma half-life data suggest that twice and possibly once daily administration of cefotetan may be clinically effective in the treatment of infections due to susceptible bacteria.

2. Cefotetan was eliminated predominantly by the kidneys, with high concentrations noted in the urine for up to 24 hours. No evidence of cefotetan accumulation in plasma or urine was found after multiple doses.

3. No metabolite of cefotetan was detected in human plasma or urine. However, small proportions of cefotetan in plasma and urine may be converted to a tautomer of cefotetan which has antibacterial activity similar to cefotetan.

4. Cefotetan was 88% plasma protein bound.

5. Diarrhea was the only significant side effect reported in normal subjects.

6. The coadministration of probenecid did not appear to offer any clinical advantage.

7. Since disulfiram-like reactions were observed in some subjects, ethanol ingestion should be avoided during and for a period after cefotetan therapy.

8. The plasma cefotetan elimination was inversely proportional to renal function. Consequently, it should be recommended that patients with creatinine clearances between 30 and 10 ml/min and $\leq$ 10 ml/min, be given half and one quarter of the standard dose of cefotetan, respectively. Alternatively, the two patient groups may be given the standard dose but at two and four times the standard dosing interval, respectively.

9. Patients requiring intermittent hemodialysis should receive a net daily dose of cefotetan of one-half of normal on the day of hemodialysis and one quarter of normal on the interdialysis days.

10. The dose of 20 mg/kg, given as an i.v. bolus to pediatric patients twice or possibly three times daily should be clinically effective in the treatment of infections due to sensitive bacteria.

11. Cefotetan rapidly penetrated the peritoneal fluid and the bile of patients without obstructed common bile ducts. Cefotetan penetrated prostatic fluid poorly. The concentrations in milk and sputum usually were less than 10% of the concurrent plasma concentrations. Cefotetan was transferred across the placenta and appeared in umbilical cord, serum, and amniotic fluid in appreciable quantities.

12. The drug rapidly penetrated a variety of solid tissues (skin, muscle and fat and otorhinolaryngological, gynecological and renal tract tissues), reaching maximal concentrations (usually within 1-2 hours) which should be therapeutic.

13. Cefotetan had no serious adverse effect on human fecal flora.

8. Detailed Review

The initial pharmacokinetic studies of cefotetan were conducted in Japan. These studies were either extended or repeated in United States or British subjects in order to assess the possibility of a racial difference in drug disposition. No significant differences were found.

The clinically significant pharmacology studies which were reviewed are listed in Table 1. Important pharmacokinetic parameters developed in these studies are listed in Table 2.

Table 1. Clinical Pharmacology Studies (Significant)

Study Identification	Ref.	Purpose	Total No. Subjects*	Dose (g)	Route	N
Yates (156 834/ 0001)	1	Pharmacokinetics, Plasma Binding, Analytical Methodology (HPLC vs. Bioassay)	10	0.25, 0.5, 1, 2 (with high fluid intake)	i.v./3 min	10
				1 (with moderate fluid intake)	i.v./3 min	10
Yates (156 834/ 0004)	2	Pharmacokinetics (Steady State After Continuous Infusion)	8	1.8	i.v./24 h	4
				1.8 (Preceded by loading dose of 0.5g i.v./3min)	i.v./24 h	4
Cohen (CEP 3-353-1)	3	Comparative Bioavailability (i.v. vs. i.m.)	12	1	i.v./30 min	12
				1	i.m.	12
Yates (156 834/ 0002)	4	Pharmacokinetics, Injection Site Discomfort	9	0 (0.5% lidocaine only)	i.m.	9
				0.5 (in water)	i.m.	9
				0.5 (in 0.5% lidocaine)	i.m.	9
Yates (156 834/ 0005)	5	Pharmacokinetics, Injection Site Discomfort	8	0 (0.5% lidocaine only) and 1 (in 0.5% lidocaine)	i.m.	2
				0 (0.5% lidocaine only) and 2 (in 0.5% lidocaine)	i.m.	2
				1 and 2 (both in 0.5% lidocaine)	i.m.	4
LaFrock (CEP 2-432-2)	6	Pharmacokinetics in Renal Failure	26 (22 renal patients, 1 hypertensive, 3 normals)	1	i.v./30 min	26

* Normal Subjects unless otherwise specified

Table 2. Pharmacokinetic Parameters[a] (Mean ± SEM) for Cefotetan in Normal Subjects

Study Identification	Ref	Dose (g)	Route	N	Plasma Conc. (µg/ml) Peak	Plasma Conc. (µg/ml) Other Time-Points	(h)	Plasma Elimination Half - Life (h)	AUC 0 - ∞ (µg/ml x h)	Urinary Recovery (% dose)	Urinary Recovery (h)	Clearance (ml/min) Plasma	Clearance (ml/min) Renal
Yates (156/834/ 0001)	1	0.25[b]	i.v./3 min	10	42 ± 3	3.0 ± 0.2	9	3.0 ± 0.1	106 ± 6	70	--[i]	40 ± 3	--
		0.5[b]	i.v./3 min	10	79 ± 5	6.0 ± 0.6	9	3.0 ± 0.2	200 ± 14	68	--[i]	43 ± 3	--
		1[b]	i.v./3 min	10	140 ± 10	12 ± 1.0	9	3.5 ± 0.2	391 ± 30	70	--[i]	46 ± 4	32
		2[b]	i.v./3 min	10	237 ± 11	22 ± 1.5	9	3.6 ± 0.2	748 ± 51	67	--[i]	48 ± 3	31
		1[c]	i.v./3 min	10	132 ± 6	11 ± 0.9	9	3.0 ± 0.1	340 ± 4	58	--[i]	--	29
Yates (156/834/ 0004)	2	1.8	i.v./24 hrs	4	37	35 ± 1.3	12	3.3 ± 0.1	---	72	48	--	--
		1.88	i.v./24 hrs	4	76	35 ± 1.2	12	3.4 ± 0.1	---	81	48	--	--
Cohen (CZF 3-353-1)	3	1	i.v./30 min	12	158 ± 6	9.0 ± 0.8	12	4.6 ± 0.3	523 ± 19[d]	61 ± 3	24	32 ± 1[e]	20 ± 1[f]
		1	i.m.	12	76 ± 3	9.0 ± 0.7	12	4.3 ± 0.2	469 ± 24[d]	51 ± 4	24	37 ± 3[e]	19 ± 2[f]
Yates (156 834/ 0002)	4	0.5	i.m.	9	23 ± 2	4.4 ± 0.4	12	3.5 ± 0.1	188 ± 12	66 ± 3	--[i]	--	32[j]
		0.5[h]	i.m.	9	23 ± 1	4.1 ± 0.4	12	3.2 ± 0.2	184 ± 9	67 ± 3	--[i]	--	--
Yates (156 834/ 0005)	5	1[h]	i.m.	6	52	9.9 ± 0.8	12	4.4	422	61	48	--	--
		2[h]	i.m.	6	91	19.3 ± 1.7	12	4.2	785	61	48	--	--

[a] In references 3-5, pharmacokinetic parameters were obtained using model-free methods. Two-compartment open models were used in references 1 and 2.
[b] Subjects on high fluid intake (mean 24-hour urine volume = 2.7L)
[c] Subjects on moderate fluid intake (mean 24-hour urine volume = 1.3L)
[d] AUC for 0-24 hours
[e] Plasma clearance calculated by dividing dose by plasma AUC
[f] Renal clearance calculated by dividing urinary recovery by plasma AUC
[g] Loading dose of 0.5g cefotetan i.v./3 min given immediately prior to 1.8g infusion
[h] Cefotetan dissolved in 0.5% lidocaine
[i] Urinary recovery obtained by determining AUC ∞ for the urinary excretion rate plot
[j] Combined data from both doses.

Specific findings from Table 2 which are important for labeling of the drug are plasma levels of cefotetan after intravenous administration (Table 3) and intramuscular administration (Table 4)

Table 3. Plasma Levels of Cefotetan After Intravenous Administration (Subjects on high fluid intake)

	Mean Concentrations (ug/ml), N = 10					
	Time After Injection (h)					
i.v. Dose	1/12	1/2	1	3	7	9
0.25 g	42	25	21	11	5	3
0.5 g	79	49	39	21	8	6
1 g	140	89	69	40	16	12
2 g	237	170	135	74	31	22

Table 4. Plasma Levels of Cefotetan After Intramuscular Administration (Cefotetan Given in 0.5% Lidocaine)

		Mean Concentrations (ug/ml), N = 12						
		Time After Injection (h)						
Ref.	i.m. Dose	1/6	1	3	5	9	12	24
4	0.5 g	4	19	23	18	8	4	
5	1 g	9	36	52	40	17	10	2
5	2 g	20	75	91	69	33	19	3

Patients with impaired renal function were studied by Dr. Jace LeFrock (reference 6 as well as Japanese investigators. The pertinent portions of these studies are summarized in Table 5.

Table 5. Pharmacokinetic Parameters (Mean ± SEM) for Cefoteton in Subjects with Varying Renal Function

Study Identification	Ref.	Dose (g)	Route	N	Creatinine Clearance* (ml/min)	Selected Cefoteton Conc.** (µg/ml)	(h)	Elimination Half-Life (h)
LeFrock (CEF 2-432-2)	6	1	i.v. / 30 min	4	> 80	6.5 ± 3.3	12	5.[illegible] ± 0.8
				12	40-80	20 ± 9	12	6.8 ± 1.0
				10	10-39	30 ± 12	12	10.1 ± 1.0
Wright and Wise	23	0.5	i.v. / 5 min	5	> 50	14	8	4.5
				3	50 - 25	24	8	7.1
				5	< 25	53	8	19
Hirano et al	26	0.5	i.v. / 3 min	8	110 - 167	8.3 ± 0.2	8	3.0 ± 0.1
				8	69 - 94	13 ± 1	8	3.7 ± 0.3
				16	31 - 58	18 ± 1	8	4.6 ± 0.4
				10	8 - 28	40 ± 4	8	11 ± 1
				7	0 - 8	46 ± 4	8	13 ± 3
Hirano et al	27	0.5	i.v. bolus	1	35	16	12	---
				1	34	37	8	---
				1	7	46	12	---
Ishino et al	28	0.5	i.v. bolus	2	95,100	4.1	12	2.7
				2	30,39	20	12	5.2
Kumeoka et al	29	0.5	i.v. bolus	1	70	9	8	---
				1	55	22	8	---
				1	52	21	8	---

*Corrected for 1.73m^2 body surface in references 6 and 26
**Plasma concentration in reference 6 and 25; serum concentration in references 26-29

II. Dosage Range Studies - Urinary Tract Infections

PROTOCOL NUMBER: 2-0-9-01

A. Investigators

Stacy J. Childs, M.D. Alabaster, AL
Rodney M. Snow, M.D. Birmingham, AL

Both investigators are qualified by training and experience to conduct investigational antimicrobial clinical trials. Dr. Childs is a urologist; and Dr. Snow is an infectious disease specialist. The study sites included two large community hospitals.

B. Detailed Design of the Study

The objectives of this study were to evaluate the safety, tolerance, and therapeutic effectiveness of intravenous cefotetan: one gram every 12 hours, compared with two grams every 24 hours, in the treatment of hospitalized adult patients with urinary tract infections due to susceptible pathogens. In addition, in those patients treated with cefotetan, information was obtained on plasma and urine concentrations of the drug.

Type of Study

This study was designed as a multicenter, controlled, randomized, non-blinded, parallel study.

C. Inclusions

Hospitalized adult male and female patients (except for nursing or pregnant females), aged 18 years and over, were entered into the study if they had a diagnosis of urinary tract infection.

D. Exclusions

Patients were excluded from the study on the basis of the following criteria:

1. Pregnant or nursing mothers.

2. History of immediate hypersensitivity reaction to penicillins or allergy to cephalosporin-type drugs.

3. Significant impairment of renal function with a serum creatinine of 2.5 mg/100 ml or greater.

4. Associated underlying disease or rapidly fatal disease which made it unlikely that treatment with the study drug or follow-up could be completed.

5. Likelihood that the patient would require therapy with antimicrobial agents, other than the study drug, during the study or follow-up periods.

E. Criteria for Evaluable Cases

1. There were appropriate pre-therapy clinical findings of urinary infection (except for cases of asymptomatic bacteriuria).

2. A pre-therapy urine culture was obtained within 48 hours before starting the study drug.

3. A specific pathogen(s) was isolated and identified from the pre-therapy urine culture.

4. The pre-therapy quantitative urine bacterial count had to be 100,000 or more bacteria per ml of urine (cases of asymptomatic bacteriuria must have had two consecutive clean void cultures containing 100,000 or more of the same organism per ml). If urine for culture was collected by suprapubic aspiration, the bacterial count had to be 5,000 or more bacteria per ml of urine.

5. In-vitro microbiologic testing did not indicate that the pathogen(s) were resistant to cefotetan.

6. If the infection had previously been treated with an antimicrobial, that drug was discontinued before obtaining the pre-therapy urine culture, and there was documentation that the previous treatment had been unsuccessful.

7. A during-therapy and post-therapy urine culture were both obtained.

8. The predetermined random schedule of drug and dosage assignment was followed.

9. The study drug had been administered long enough to allow a judgment as to its effect or lack of effect (minimum of 48 hours)

10. No antimicrobial, other than the study drug, had been administered from the time of pre-therapy urine culture until after the post-therapy urine culture was obtained.

11. No underlying condition or disease obscured or prevented evaluation of the patient's response to study drug treatment.

Efficacy:

Bacteriological Response

Bacteriologic response was assessed on the basis of quantitative urine cultures which were obtained: 1) on the second to fourth day of treatment; and 2) five to nine days after stopping the study drug. Additional cultures were to be obtained at the end of therapy.

The endpoints for bacteriological response were:

Cure: urine culture was negative for the initial pathogen (or there were 10,000 or less organisms per ml of urine or a sterile urine if collected by suprapubic aspiration) at 2 to 4 days during therapy and through 5 to 9 days after therapy.

Failure: urine culture shows counts of the initial pathogen in a concentration greater than 10,000 organisms per ml of urine (any number of organisms present from a suprapubic aspiration) at 2 to 4 days during therapy and/or up to 9 days after therapy.

Cure with Superinfection or Failure with Superinfection: one of the above plus isolation of one or more new pathogens from urine culture during therapy and for up to 9 days after therapy.

Clinical Response

The patient's clinical response to treatment was classified according to the following definitions:

Infection completely cleared: clinical signs and symptoms of the urinary infection disappeared with treatment.

Infection improved: clinical signs or symptoms of the urinary infection substantially improved with treatment.

Infection unchanged or worse: clinical signs or symptoms of the urinary tract infection were substantially unchanged or worse with treatment.

Unable to evaluate: for asymptomatic bacteriuria patients, when no evaluation of clinical response could be made.

F. Evaluable Patients

Thirty-six of 52 patients were evaluable. Exclusions were primarily for either resistant pathogens pre-therapy or insufficient colony count pre-therapy.

The bacteriological response to treatment is given in Table 1.

Table 1 Bacterial Response to Treatment Related to Pathogens

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response			
			Cure	Cure with Superfection	Failure	Failure with Superinfection
Cefotetan 1 gm	Escherichia coli	13	11	2	0	0
	Klebsiella pneumoniae	1	1	0	0	0
	Citrobacter diversus	1	1	0	0	0
	Diptheroids	1	1	0	0	0
	Proteus mirabilis	1	1	0	0	0
	Streptococcus viridans	1	1	0	0	0
	Polymicrobial	1	0	1	0	-
	Total	19	16 (84%)	3 (16%)	0 (0%)	0 (0%)
Cefotetan 2 gm	Escherichia coli	14	11	1	2	0
	Citrobacter species	1	0	0	1	0
	Polymicrobial	2	2	1	0	-
	Total	17	13 (6%)	0 (6%)	3 (18%)	0 (0%)

C. Conclusions

In this multicenter study comparing two dosage regimens of cefotetan in hospitalized adults, intravenous cefotetan administered as either one gram every 12 hours or two grams every 24 hours, was comparable in effectiveness for the treatment of both complicated and uncomplicated bacterial urinary tract infections due to susceptible pathogens. Intravenous cefotetan therapy was well tolerated with similar types of non-serious adverse effects occurring with both dosage regimens.

III. CONTROLLED STUDIES

A. Urinary Tract Infections

1. Protocol number: 2-0-1-01. A multicenter comparative study of intravenous cefotetan and cefoxitin in the treatment of hospitalized patients with urinary tract infection.

a. Investigators

Stacy J. Childs, M.D.	Birmingham, AL
Clair E. Cox, M.D.	Memphis, TN
Charles P. Craig, M.D./ Bienvendio Yangco, M.D.	Tampa, FL
David M. Drylie, M.D.	Gainesville, FL
William J. Holloway, M.D.	Wilmington, DE
Willis P. Jordan, M.D.	Memphis, TN
J. Peter Rissing, M.D.	Augusta, GA
Rodney M. Snow, M.D.	Birmingham, AL

The study sites included four Veteran Administration hospitals, two large teaching university medical centers, and three large community hospitals.

b. Design of the Study

Objectives

The objectives of this study were to evaluate the therapeutic effectiveness, safety and tolerance of intravenous cefotetan administered twice daily (every 12 hours), compared with cefoxitin administered three times daily (every 8 hours), in the treatment of hospitalized adult patients with urinary tract infections due to susceptible pathogens. In addition, for patients treated with cefotetan, information on plasma and urine concentrations of the drug were to be obtained. Based on the patient's condition and the severity of infection, patients were stratified into a low dose and high dose group. Then, low dose patients were randomized to treatment with either: cefotetan, 1 gm intravenously every 12 hours (2 gms

daily), or cefoxitin, 1 gm intravenously every 8 hours (3 gms daily). High dose patients were randomized to treatment with either: cefotetan, 2 gm intravenously every 12 hours (4 gms daily), or cefoxitin 2 gm intravenously every 8 hours (6 gms daily). Within each randomization, patients were assigned to cefotetan or cefoxitin in a 2 to 1 ratio favoring cefotetan. Most patients were treated for 5 to 10 days.

Type of Study

This study was designed as a multicenter, controlled, non-blinded, parallel study.

Inclusion and Exclusion Criteria

These criteria were identical to those for the urinary tract study reviewed under Dose Range Studies-Urinary Tract Infections.

Evaluability and Efficacy Criteria

These criteria were identical to those for the urinary tract study reviewed under Dose Range Studies- Urinary Tract Infections.

c. Evaluable Patients

Of 523 patients entered into this study, 382 were evaluable. The evaluable patients by investigator are listed in Table 1.

Table 1 Number of Evaluable and Non Evaluable Cases By Investigator

Investigator	Total No. of Pts.	Randomized Study Drug Cefotetan Evaluable	Non-Evaluable	Total	Randomized Study Drug Cefoxitin Evaluable	Non-Evaluable	Total
Dr. Childs	70						
1 gram/dose		14	3	17	6	4	10
2 grams/dose		20	8	28	11	4	15
Dr. Cox	118						
1 gram/dose		70	2	72	36	1	37
2 grams/dose		4	2	6	3	0	3
Drs. Craig/Yangco	46						
1 gram/dose		8	12	20	6	4	10
2 grams/dose		2	9	11	0	5	5
Dr. Drylie	30						
1 gram/dose		15	5	20	8	2	10
Dr. Holloway	50						
1 gram/dose		17	5	22	8	3	11
2 grams/dose		9	3	12	4	1	5
Dr. Jordan	118						
1 gram/dose		69	9	78	32	8	40
Dr. Riesing	11						
1 gram/dose		2	3	5	1	3	4
2 grams/dose		1	1	2	0	0	0
Dr. Snow	80						
1 gram/dose		15	12	27	5	8	13
2 grams/dose		12	13	25	4	11	15
Total	523						
1 gram/dose		210	51	261	102	33	135
2 grams/dose		48	36	84	22	21	43

d. Patient Characteristics

All patient were hospitalized. For both treatment groups, the populations tended to be older aged, approximately two-thirds were 60 or more years of age. Mean ages were 62 and 61 years, respectively. Approximately two-thirds were men and one-third women for both drug groups. Whites constituted 56% and 57% of the population, respectively, and blacks 44% and 42%, respectively. There was one hispanic in each drug group.

The general condition of patients at the time of entry into the study was judged by the investigator to be fair, poor or critical in 44% of the cefotetan group and 50% of the cefoxitin group. The status of renal function as clinically judged by the investigator, was reported to be normal in 82% of both treatment groups. Mild impairment was reported in another 15% and 13%, respectively, and moderate renal impairment in another 3% and 6%, respectively. In addition to clinical judgment of renal function, pre-therapy serum creatinine levels were obtained in most patients. Creatinine levels were 2.5 mg % or more in only 4% of both groups. Therefore, renal function was essentially normal for most patients in each group.

The types of clinical infection were: urinary tract infection-not otherwise specified, pyelonephritis, cystitis, prostatitis and asymptomatic bacteriuria.

One or more underlying structural or functional abnormality of the genitourinary tract; or urologic surgery or instrumentation during the treatment period; or an indwelling urinary catheter, were present in 82% and 85% of the drug groups, respectively. In addition, most patients also had one or more other significant underlying diseases. Most frequent were cardicvascular diseases, bronchopulmonary diseases, malignancy, and diabetes mellitus. Only 29% and 21% of each drug group did not have other significant underlying diseases.

e. Reasons for excluding non-evaluable cases

Of 523 patients entered, 141 were excluded (cefotetan-51 patients 1 gram dose, 36 patients 2 grams; cefoxitin-33 patients 1 gram dose, 21 patients 2 grams). The most frequent reasons for exclusion were no pathogen isolated pre-therapy (20 pts), resistant pathogen isolated pre-therapy (31 patients), and no culture obtained post-therapy (16 pts). These reasons were evenly distributed in the dosage regimens studied.

f. Efficacy

The following tables 2-5 represent the sponsor's efficacy summary. This reviewer found the following additional

patients unevaluable for efficacy. Their exclusion does not alter the overall results of this study, but these patients have been excluded from the overall efficacy summary given at the conclusion of this NDA review.

Additional patients excluded from efficacy analysis

PAGE NO.	PATIENT NO.	DRUG	REASON FOR NON-EVALUABILITY
11	9	CFX	No post-Rx culture obtained
11	12	CTN	No post-Rx culture obtained
13	22	CFX	Less than five days treatment
15	34	CTN	No post-Rx culture obtained
18	54	CFX	No post-Rx culture obtained
18	57	CFX	Less than five days treatment
25	101	CFX	No post-Rx culture obtained
28	209	CTN	No post-Rx culture obtained
30	17	CFX	No post-Rx culture obtained
37	3	CTN	No post-Rx culture obtained
44	5	CTN	Less than five days treatment
47	27	CFX	Less than five days treatment
49	37	CTN	Less than five days treatment
54	69	CTN	No post-Rx culture obtained
66	28	CTN	No post-Rx culture obtained

Table 2. Bacteriological Response to Low Dose Treatment Related to Pathogens

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response: Cure	Cure with Superinfection	Failure	Failure with Superinfection
Cefotetan (Low Dose)	Escherichia coli	125	108	10	5	2
	Klebsiella species	1	1	0	0	0
	Klebsiella pneumoniae	38	30	8	0	0
	Klebsiella oxytoca	1	1	0	0	0
	Klebsiella oxaenae	1	1	0	0	0
	Enterobacter aerogenes	1	1	0	0	0
	Enterobacter cloacae	3	0	3	0	0
	Proteus mirabilis	22	19	3	0	0
	Proteus vulgaris	1	1	0	0	0
	Providencia rettgeri	3	1	2	0	0
	Providencia stuartii	2	2	0	0	0
	Staphylococcus epidermidis	1	1	0	0	0
	Polymicrobial	11	4	6	1	0
	Total	210	170 (81%)	32 (15%)	6 (3%)	2 (1%)
Cefoxitin (Low Dose)	Escherichia coli	69	47	8	13	1
	Klebsiella species	1	0	1	0	0
	Klebsiella pneumoniae	14	10	2	2	0
	Proteus mirabilis	12	7	3	2	0
	Proteus vulgaris	2	1	0	1	0
	Streptococcus agalactiae	1	1	0	0	0
	Polymicrobial	3	1	1	1	0
	Total	102	67 (65%)	15 (15%)	19 (19%)	1 (1%)

Table 3. Bacteriological Response to High Dose Treatment Related to Pathogens

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response			
			Cure	Cure with Superinfection	Failure	Failure with Superinfection
Cefotetan (High Dose)	Escherichia coli	33	22	9	1	1
	Klebsiella species	1	0	0	0	1
	Klebsiella pneumoniae	5	2	1	0	2
	Enterobacter aerogenes	1	1	0	0	0
	Proteus mirabilis	4	2	2	0	0
	Providencia rettgeri	1	1	0	0	0
	Polymicrobial	3	1	2	0	0
	Total	48	29 (60%)	14 (29%)	1 (2%)	4 (9%)
Cefoxitin (High Dose)	Escherichia coli	16	12	3	1	0
	Klebsiella pneumoniae	3	2	1	0	0
	Proteus species	1	0	0	1	0
	Proteus mirabilis	1	0	1	0	0
	Morganella morganii	1	1	0	0	0
	Total	22	15 (68%)	5 (23%)	2 (9%)	0

Table 4. Bacteriological Response of Uncomplicated and Complicated Infections

Treatment	Number of Evaluable Cases	Bacteriological Response			
		Cure	Cure with Superinfection	Failure	Failure with Superinfection
Uncomplicated Infections					
Low Dose					
Cefotetan	54	47 (87%)	6 (11%)	1 (2%)	0
Cefoxitin	24	20 (83%)	0	3 (13%)	1 (4%)
High Dose					
Cefotetan	26	18 (69%)	5 (19%)	0	3 (12%)
Cefoxitin	13	9 (69%)	2 (15%)	2 (15%)	0
Overall					
Cefotetan	80	65 (81%)	11 (14%)	1 (1%)	3 (4%)
Cefoxitin	37	29 (78%)	2 (5%)	5 (14%)	1 (3%)
Complicated Infections					
Low Dose					
Cefotetan	156	123 (79%)	26 (17%)	5 (3%)	2 (1%)
Cefoxitin	78	47 (60%)	15 (19%)	16 (21%)	0
High Dose					
Cefotetan	22	11 (50%)	9 (41%)	1 (5%)	1 (5%)
Cefoxitin	9	6 (67%)	3 (33%)	0	0
Overall					
Cefotetan	178	134 (75%)	35 (20%)	6 (3%)	3 (2%)
Cefoxitin	87	53 (61%)	18 (21%)	16 (18%)	0

Table 5 . Clinical Response

Treatment	Number of Evaluable Patients	Completely Cleared	Improved	Unchenged or Worse
Cefotetan	255	221 (87%)	27 (10%)	7 (3%)
Cefoxitin	122	94 (77%)	21 (17%)	7 (6%)
Low Dose				
Cefotetan	207	177 (86%)	23 (11%)	7 (3%)
Cefoxitin	100	76 (76%)	18 (18%)	6 (6%)
High Dose				
Cefotetan	48	44 (92%)	4 (8%)	0
Cefoxitin	22	18 (82%)	3 (14%)	1 (4%)

Table 6 . Plasma and Urine Levels of Cefotetan

Dosage	Plasma Concentrations (mcg/ml)				Urine Concentrations (mcg/ml)	
	Peak		Trough			
	Number of Patients	Mean	Number of Patients	Mean	Number of Patients	Mean
1 Gram every 12 hrs.	139	101.6	139	17.3	118	703.2
2 Grams every 12 hrs.	30	180.0	29	27.9	33	1715.6

g. Safety

In this study of 523 patients, 150 adverse effects were reported with cefotetan (90 clinical effects and 60 abnormal laboratory values) and 79 with cefoxitin (44 clinical and 35 laboratory). Of these, 28 reactions (25 clinical and 3 laboratory) were considered to be cefotetan-related, and 5 clinical reactions cefoxitin related.

Local Reactions

cefotetan - 6 (discomfort at injection site, swelling, phlebitis)

cefoxitin - 4 (discomfort at injection site, swelling, redness)

Hypersensitivity Reactions

cefotetan - 6 (chills, itching, erythema, rash) - 4 patients discontinued because of reaction

cefoxitin - 1 - rash with itching

Gastrointestinal Reactions

cefotetan - 11 (diarrhea) - 3 patients discontinued

cefoxitin - none

Hematologic abnormalities

cefotetan - 3 (eosinophila, neutropenia, increased prothrombin time) - no discontinuations.

cefoxitin - none

h. Conclusions

In this multicenter study comparing cefotetan and cefoxitin in hospitalized adults, intravenous cefotetan, administered less frequently (every 12 hours, versus every 8 hours) and at a lower total daily dose (2 or 4 grams, versus 3 or 6 grams) than cefoxitin, was comparable in effectiveness to cefoxitin in the treatment of both complicated and uncomplicated bacterial urinary tract infections due to susceptible pathogens. However, overall and for infections caused by E. coli, one gram dose cefotetan were significantly more effective than one gram doses of cefoxitin, particularly for complicated infections. These differences were statistically significant.

Intravenous cefotetan therapy was well tolerated. Similar types of non-serious adverse effects occurred with both drugs, although diarrhea occurred more frequently with cefotetan.

Cefotetan produced high and prolonged plasma levels and urinary concentrations of drug with dosing every 12 hours.

It is concluded that cefotetan, one or two grams given intravenously every 12 hours, is effective and safe in the treatment of both complicated and uncomplicated urinary tract infections caused by susceptible pathogens.

2. Protocol number 2-0-1-02. A multicenter comparative study of intravenous cefoxitin and two dosage regimens of cefotetan in the treatment of hospitalized patients with urinary tract infections.

a. Investigators

Clair E. Cox, M.D.	Memphis, TN
Charles P. Craig, M.D./ Bienvenido Yangco, M.D.	Tampa, FL
Glen W. Wells, M.D.	Birmingham, AL

The study sites included two Veteran Administration hospitals, one large teaching university medical center, and one large community hospital.

b. Design of the Study

Objectives

The objectives of this study were to evaluate the safety, tolerance, and therapeutic effectiveness of intravenous cefotetan: 0.5 grams every 12 hours and one gram once-daily, compared with one gram every 8 hours of intravenous cefoxitin (Mefoxin^{R}), in the treatment of hospitalized adult patients with urinary tract infections due to susceptible pathogens. In addition, in those patients treated with cefotetan, information was obtained on plasma and urine concentrations of the drug.

Type of Study

This study was designed as a multicenter, controlled, non-blinded, parallel study.

Inclusion and Exclusion Criteria

The criteria were identical to those used in the previously reviewed urinary tract infections studies.

Evaluability and Efficacy Criteria

These criteria were identical to those used in the previously reviewed urinary tract infection studies.

c. Evaluable Patients

Of 216 patients entered into the study, 164 were evaluable. The evaluable patients by investigator are listed in Table 1.

Evaluable patient by Investigator

Investigator	Total No. of Pts.	Randomized Study Drug Cefotaxime			Randomized Study Drug Cefazolin		
		Evaluable	Non-Evaluable	Total	Evaluable	Non-Evaluable	Total
Dr. Cox/CEF 2-409-3	53						
0.5 gram/dose		16	2	18			
1.0 gram/dose		19	1	20	14	1	15
Dr. Cox/CEF 2-409-4	69						
0.5 gram/dose		23	3	26			
1.0 gram/dose		24	1	25	17	1	18
Dr. Craig/CEF 2-440-2	74						
0.5 gram/dose		14	14	28			
1.0 gram/dose		13	14	27	8	11	19
Dr. Wells/CEF 2-472-1	20						
0.5 gram/dose		5	2	7			
1.0 gram/dose		7	1	8	4	1	5
Total	216						
0.5 gram/dose		58	21	79			
1.0 gram/dose		63	17	80	43	14	57

Table 1.

d. Patient Characteristics

All patients were hospitalized. For both treatment groups, the populations tended to be older aged, approximately three-quarters of the cefotetan patients and 61% of the cefoxitin patients were 60 or more years of age. Mean ages were 63 and 61 years, respectively. Approximately 80% were men and 20% women for both drug groups. Whites constituted 58% and 58% of the population, respectively, and blacks 42% and 41%, respectively.

The general condition of patients at the time of entry into the study was judged by the investigator to be fair or poor in 48% of the cefotetan group and 34% of the cefoxitin group. The status of renal function as clinically judged by the investigator, was reported to be normal in 86% of the cefotetan group and 79% of the cefoxitin group. Mild impairment was reported in another 8% and 11%, respectively, and moderate renal impairment in another 3% and 5%, respectively. One patient in each group was reported to have severe renal impairment. In addition to clinical judgment of renal function, pre-therapy serum creatinine levels were obtained in most patients. Creatinine levels were 2.5 mg % or more in only 4% of both groups. Therefore, renal function was essentially normal for most patients in each group.

The types of clinical infection were: urinary tract infection-not otherwise specified, pyelonephritis, cystitis, prostatitis and asymptomatic bacteriuria.

One or more underlying stuctural or functional abnormality of the genitourinary tract; or urologic surgery or instrumentation during the treatment period; or an indwelling urinary catheter, were present in the majority of each group. In addition, most patients also had one or more other significant underlying diseases. Most frequent were cardiovascular diseases.

e. Reasons for excluding non-evaluable cases

Of 216 adult patients entered, 52 were excluded-21 cefotetan 0.5 gram, 17 cefotetan 1.0 gram, and 14 cefoxitin 1.0 gram dose. The most frequent reasons for exclusion were resistant pathogen isolated pre-therapy (11), insufficient colony count pre-therapy (8), and other antibiotic administered after therapy and before post-therapy culture (8).

f. Efficacy

The following tables 2-5 represent the sponsor's efficacy summary. This reviewer found the following additional patients

unevaluable for efficacy. Their exclusion does not alter the overall results of this study, but these patients have been excluded form the overall efficacy summary at the conclusion of this NDA review.

Additional patients excluded from efficacy analysis

Page No.	Patient No.	Drug	Reason for Non-Evaluability
127	63	CTN	Less than five days treatment
135	59	CTN	No post-Rx culture obtained
136	73	CTN	No post-Rx culture obtained

Table 2 . Bacteriological Response (All Evaluable Cases)

Treatment	Number of Evaluable Cases	Bacteriological Response			
		Cure	Cure with Superinfection	Failure	Failure with Superinfection
Cefotetan	121	89 (74%)	19 (16%)	10 (8%)	3 (2%)
Cefoxitin	43	34 (79%)	7 (16%)	2 (5%)	0 (0%)
Cefotetan 0.5 gm	58	44 (76%)	9 (16%)	3 (5%)	2 (3%)
Cefotetan 1.0 gm	63	45 (71%)	10 (16%)	7 (11%)	1 (2%)
Cefoxitin 1.0 gm	43	34 (79%)	7 (16%)	2 (5%)	0 (0%)

Table 3

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response: Cure	Cure with Superinfection	Failure	Failure with Superinfection
Cefotetan 0.5 gm	Escherichia coli	34	28	5	1	0
	Klebsiella species	6	1	3	2	0
	Klebsiella pneumoniae	7	7	0	0	0
	Enterobacter cloacae	1	0	1	0	0
	Citro diversus	1	0	0	0	1
	Proteus mirabilis	8	7	0	0	1
	Polymicrobial	1	1	0	0	0
	Total	58	44 (76%)	9 (16%)	3 (5%)	2 (3%)
Cefotetan 1.0 gm	Escherichia coli	37	28	4	4	1
	Klebsiella species	1	0	1	0	0
	Klebsiella pneumoniae	5	4	1	0	0
	Enterobacter species	1	0	1	0	0
	Proteus mirabilis	12	13	3	2	0
	Total	63	45 (71%)	10 (16%)	7 (11%)	1 (2%)
Cefoxitin 1.0 gm	Escherichia coli	30	25	3	2	0
	Klebsiella species	1	0	1	0	0
	Klebsiella pneumoniae	4	3	1	0	0
	Proteus mirabilis	4	3	1	0	0
	Proteus vulgaris	1	1	0	0	0
	Providencia rettgeri	1	1	0	0	0
	Pseudomonas capacia	1	1	0	0	0
	Polymicrobial	1	0	1	0	0
	Total	43	34 (79%)	7 (16%)	2 (5%)	0 (0%)

Table 4

Treatment	Number of Evaluable Cases	Bacteriological Response			
		Cure	Cure with Superinfection	Failure	Failure with Superinfection
Uncomplicated Infections					
Cefotetan 0.5 gm	13	6 (46%)	4 (31%)	2 (15%)	1 (8%)
Cefotetan 1.0 gm	15	11 (74%)	2 (13%)	2 (13%)	0 (0%)
Cefoxitin 1.0 gm	4	3 (75%)	0 (0%)	1 (25%)	0 (0%)
Overall					
Cefotetan	28	17 (61%)	6 (21%)	4 (14%)	1 (4%)
Cefoxitin	4	3 (75%)	0 (0%)	1 (25%)	0 (0%)
Complicated Infections					
Cefotetan 0.5 gm	43	38 (85%)	5 (11%)	1 (2%)	1 (2%)
Cefotetan 1.0 gm	48	34 (71%)	8 (17%)	5 (10%)	1 (2%)
Cefoxitin 1.0 gm	39	31 (79%)	7 (18%)	1 (3%)	0 (0%)
Overall					
Cefotetan	93	72 (77%)	13 (14%)	6 (7%)	2 (2%)
Cefoxitin	39	31 (79%)	7 (18%)	1 (3%)	0 (0%)

Table 5. Clinical Response (All Evaluable Cases)

Treatment	Number of Evaluable Patients	Clinical Response		
		Completely Cleared	Improved	Unchanged or Worse
Cefotetan	121	110 (91%)	8 (7%)	3 (2%)
Cefoxitin	43	38 (88%)	5 (12%)	0
Cefotetan 0.5 gm	58	56 (97%)	2 (3%)	0
Cefotetan 1.0 gm	63	54 (86%)	6 (9%)	3 (5%)
Cefoxitin 1.0 gm	43	38 (88%)	5 (12%)	0

g. Safety

In this study of 216 patients, 46 adverse effects were reported with cefotetan (15 clinical effects and 31 abnormal laboratory values) and 12 with cefoxitin (7 clinical and 5 laboratory). Of these, 4 effects (1 clinical and 3 laboratory) were cefotetan related, and 2 clinical effects were cefoxitin related.

Cefotetan was discontinued in one patient because of nausea and vomiting and in one patient because of phlebitis.

Local reactions

cefotetan - 1 cellulitis at injection site

Hypersensitivity reactions

cefoxitin - 1 itching

Central Nervous System Reactions

cefoxitin - flushing

Hepatic abnormal lab values

cefotetan - 3 (SGOT, SGPT, LDH elevations)

h. Conclusions

In this multicenter study comparing cefoxitin and two dosage regimens of cefotetan in hospitalized adults, intravenous cefotetan, administered less frequently (every 12 or 24 hours, versus 3 grams), was comparable in effectiveness to cefoxitin in the treatment of both complicated and uncomplicated bacterial urinary tract infections due to susceptible pathogens.

Intravenous cefotetan therapy was well tolerated. Similar types of non-serious adverse effects occurred with both drugs.

Cefotetan produced high and prolonged plasma levels and urinary concentrations of drug with dosing every 12 hours, as well as every 24 hours.

It is concluded that intravenous cefotetan, 0.5 gram every 12 hours or 1.0 gram once-daily, is effective and safe in the treatment of complicated and uncomplicated urinary tract infections caused by susceptible pathogens.

B. Lower Respiratory Tract Infection Controlled Studies

1. Protocol 2-1-2-01. A multicenter comparative study of parenteral cefotetan and moxalactam in the treatment of hospitalized patients with lower respiratory tract infections.

a. Investigators

Michael A. Castellano, M.D.	New York, N.Y.
P. Craig, M.D./ Bienvenido Yangco, M.D.	Tampa, FL
Ronald W. Geckler, M.D.	Baltimore, MD
Paul M. Kaihlanen, M.D.	San Antonio, TX
Alex T. Makris, M.D.	Camden, NJ
Thomas Nolen, M.D.	Alabaster, AL
John J. Seidenfeld, M.D.	Tucson, AZ
James S. Tan, M.D.	Akron, OH

The study sites included two Veterans Administration hospitals and six large community hospitals. All nine investigators used an identical protocol.

b. Design of the Study

Objectives

The objectives of this study were to evaluate the safety, tolerance and therapeutic effectiveness of a twice-daily (every 12 hours) dosing regimen of parenteral cefotetan compared with parenteral moxalactam (every 8 hours), in the

treatment of hospitalized adult patients with lower respiratory tract infections due to susceptible pathogens. In addition plasma and urine concentrations of cefotetan were to be obtained.

The study was designed as a controlled, randomized, non-blinded, parallel study. Before each participating medical center began entering patients into the study, the appropriate institutional review committee reviewed and approved the study. Written informed consent was obtained from each patient before they were entered into the study.

Hospitalized adult patients with symptoms and signs of a lower respiratory infection who were likely to meet all the entry criteria were identified. Respiratory tract infections were to be confirmed by appropriate clinical findings, presence of appropriate pulmonary findings on chest x-ray, and isolation and identification of pathogen(s) to genus and species. The pathogen(s) were determined to be susceptible to the study drug by disk testing using the Kirby-Bauer method and/or MIC determination.

Specific entry criteria were the following:

1. Patients were to have a clinical diagnosis of lower respiratory tract injection.

2. Age: 18 years and older.

3. Both males and females were included except for nursing or pregnant females.

4. If a patient was receiving antimicrobial therapy, it had to be discontinued prior to obtaining the pre-therapy cultures. Patients could not receive any antimicrobial therapy, other than the study drug, from the time that the pre-therapy culture had been obtained until the end of therapy culture had been obtained or the patient would not be evaluable for efficacy.

5. Lower respiratory tract infections were required to be confirmed by isolation and identification of pathogen(s) and by a chest x-ray.

   If necessary, therapy was permitted to be initiated prior to the culture and/or x-ray results. For the patient to remain in the study, the pathogens(s) had to be susceptible to cefotetan and the chest x-ray confirmed the diagnosis of a lower respiratory infection. Susceptibility to the cefotetan was determined by standard disk diffusion testing using 30 microgram disks of cefotetan, and/or MIC determinations.

Exclusion Criteria:

1. Pregnant or nursing mothers.

2. History of an immediate hypersensitivity reaction to penicillins or allergy to cephalosporin-type agents.

3. Known or suspected significant renal function impairment with a serum creatinine of 2.5 mg % or greater.

4. Associated underlying disease or rapidly fatal disease which made it unlikely that treatment with the study drug could be completed.

5. Likelihood that the patient would require therapy with antimicrobial agents other than the study drug during the study.

6. Identifiable risk of life-threatening pseudomonas disease; e.g., patients with acute leukemia and granulocytopenia.

7. Evidence of CNS infectious disease.

Withdrawal Criteria:

A patient was to be removed from the study for any of the following reasons:

1. No pathogen was isolated pre-therapy.

2. The pathogen was resistant to the study drug assigned to the patient.

3. The patient developed a serious medical condition that the investigator thought made it unwise to continue.

4. The patient developed a serious or alarming adverse reaction to the study drug.

5. The investigator judged that the study drug should be discontinued because of an exacerbation of the patient's disease.

6. Any reason, if the investigator thought it was in the best interest of the patient.

7. The patient wanted to withdraw from the study.

Evaluability and Efficacy Criteria

Sputum, pleural fluid, transtracheal aspirate or other appropriate material, and blood for bacteriological culture were to be obtained prior to the start of the study drug. Prior to culture, sputum samples were evaluated for acceptability. A gram stained smear of the sputum was to be examined microscopically at 100X and only samples with $\leq$ 10 squamous epithelial cells were to be considered appropriate for culture. Treatment could begin before results of the bacteriological studies were known. However, when these results became available, if no pathogen was isolated or if the pathogen was resistant to the study drug, the drug was to be discontinued.

Treatment with cefotetan and moxalactam was to be by the intravenous route only. Patients were assigned to either cefotetan every 12 hours or moxalactam every 8 hours according to a predetermined randomization schedule provided by Stuart. Each investigator was given a series of consecutively numbered, sealed envelopes. Patients were assigned, in order to entry into the study, to the next numbered envelope for that randomization. A label inside the envelope identified the study medication and it was attached to the patient's case report form. Patients were assigned to these drugs in a ratio of 2:1 (twice as many patients were assigned to cefotetan as moxalactam). Based on the severity of the patient's infection the investigator determined the dosage of study drug. Cefotetan dosage was either 2 or 3 grams every 12 hours, moxalactam dosage was 1 or 2 grams every 8 hours. Duration of therapy was to be for a minimum of five days, with continuation at the discretion of the investigator, based on the patient's general condition, underlying disease, severity of infection and patient's response to treatment. No other concomittant antimicrobial therapy was permitted. Other necessary medications were permitted and were recorded on the case report form.

During treatment, sputum cultures were obtained as appropriate; if the pretreatment blood culture was positive, a repeat blood culture was to be obtained 2-4 days after the start of the study drug. Within 24 hours of completion of therapy a follow-up sputum culture was to be obtained, if possible. A follow-up blood culture was to be obtained if it had previously been positive.

A daily clinical assessment was made for local tolerance to the intravenous injections, and any adverse effects. Appropriate laboratory tests to evaluate hematologic, hepatic and renal abnormalities were to be performed before study drug treatment began and at the end of treatment. If treatment was prolonged, these were to be repeated at no less than one week intervals. Any abnormal laboratory test was to be followed up appropriately.

For patients treated with cefotetan, whenever possible, plasma and urine specimens were to be obtained on the second, third or fourth day of therapy to measure cefotetan levels by HPLC.

c. Evaluable Patients

Of 252 patients studied, 161 were evaluable (111 treated with cefotetan and 50 with moxalactam). The evaluable patients by investigator are listed in the following Table 1.

Table 1

Investigator	Evaluable/Total Patients
Casteliano	8/13
Craig	7/15
Geckler	18/33
Kaihlanen	11/28
Makris	1/4
Nolen	81/98
Seidenfeld	20/41
Tan	15/20

d. Patient Characteristics

A total of 252 hospitalized adult patients were entered into this study by nine investigators at eight sites within the United States.

The primary diagnosis for all patients was lower respiratory tract infection, confirmed by appropriate clinical findings, isolation and identification of a pathogen and presence of appropriate pulmonary findings on chest x-ray.

For both treatment groups, the populations were primarily older (mean 63.8 cefotetan, 66.7 moxalactam), white (83% cefotetan, 78% moxalactam) and male (68% cefotetan, 62% moxalactam). Each treatment group consisted primarily of patients whose general condition was fair (57% cefotetan, 56% moxalactam) and whose infection had been present for 5 days or more (54% cefotetan, 55% moxalactam). The status of renal function as clinically judged by the investigator, was reported to be normal in 86% of the cefotetan groups and 83% of the moxalactam group. In addition to clinical judgement of renal function, pre-therapy serum creatinine levels were obtained in most patients. Creatinine levels were 2.5 mg% or more in approximately 2% of both groups. Therefore, renal function was essentially normal for most patients in each group.

The most common prim[illegible]osis was pneumonia (90% of the cefotetan treated pc[illegible], 87% moxalactam population). Eighty-eight percent [illegible]the cefotetan population and 87% of the moxalactam patients had other underlying diseases. Hospital acquired infections were seen in 21% of the cefotetan patients and in only 12% of the moxalactam treated patients. Sixteen percent of the cefotetan group and 17% of the moxalactam group received unsuccessful prior antimicrobial therapy. Approximately 75% of the cefotetan patients and 71% of the moxalactam patients were treated for 5-10 days.

e. Reasons for excluding non-evaluable cases

Of the 252 patients entered in this study, 91 were found unevaluable. The reasons are given in the following Table 2.

Table 2. Reason for Non-Evaluability

Reason for Exclusion	Cefotetan	Moxalactam
No pathogen isolated pre-therapy	39	26
Resistant pathogen isolated pre-therapy	7	2
X-ray non-confirmatory for LRI	4	0
Treatment period less than 48 hours	3	1
No follow-up chest x-ray	2	0
No appropriate clinical findings for LRI	0	1
No pre-therapy cultures	0	1
No follow-up cultures	2	0
Other antimicrobial given before therapy	0	1
Other antimicrobial given during therapy	1	0
Patient developed serious medical condition	1	0
Total Number of Patients	59	32

f. The following tables 3-6 represent the sponsor's efficacy summary. This reviewer found the following additional patients unevaluable for efficacy. Their exclusion does not alter the overall results of this study, but these patients have been excluded from the overall efficacy summary at the conclusion of this NDA review.

Additional patients excluded from efficacy analysis

Page No.	Patient No.	Drug	Reason for Non-Evaluability
174	7	MOX	Less than five days treatment
178	14	MOX	Less than five days treatment
179	20	CTN	Less than five days treatment
202	3	CTN	Sensitivities not obtained

In additon, the following changes were made.

Page No.	Patient No.	Drug	Changes made
180	22	CTN	Bact Resp. changed to UNSAT

Table 3 . Bacteriologic Response

Type of Reaction	Number of Evaluable Patients C	M	Satisfactory with end culture C	M	Satisfactory no end culture C	M	Unsatisfactory C	M
Gram Negative								
Branhamella catarrhalis	1	1	0	1	1	0	0	0
Citrobacter diversus	1	0	1	0	0	0	0	0
Citrobacter freundii	2	0	0	0	1	0	1	0
Enterobacter aerogenes	1	0	0	0	0	0	1	0
Enterobacter cloacae	4	1	3	1	0	0	1	0
Enterobacter sp.	1	0	0	0	1	0	0	0
E. coli	7	6	6	4	1	2	0	0
H. influenzae	16	11	12	5	2	6	2	0
H. haemolyticus	1	0	0	0	1	0	0	0
H. parainfluenza	1	0	1	0	0	0	0	0
Klebsiella oxytoca	2	0		0	0	0	0	0
Klebsiella ozaenae	1	0	1	0	0	0	0	0
Klebsiella pneumoniae	8	4	7	3	1	1	0	0
Moraxella sp.	1	0	1	0	0	0	0	0
Proteus mirabilis	2	2	2	1	0	0	0	1
Pseudomonas aeruginosa	0	1	0	0	0	1	0	0
Pseudomonas fluorescens	0	1	0	1	0	0	0	0
Serratia marcescens	3	0	1	0	1	0	1	0
Total	52	27	37	15	9	10	6	1
Gram Positive								
Staphyloccus aureus	8	4	7	3	1	1	0	0
Streptococcus pneumoniae	24	9	16	9	5	0	3	0
Total	32	13	23	12	6	1	3	0
Polymicrobial (Number of Patients)	26	10	14	8	9	1	3	1
No growth, Positive Quellung, spt S. pneumoniae, blood	1	0	1	0	0	0	0	0
Total	111	50	75	36	24	12	12	2

C = cefotetan M = moxalactam

Table 4. Response Summary for Pathogens in Patients with Polymicrobial Infections

Pathogen	Number of Pathogens Isolated C	M	Satisfactory with end culture C	M	Satisfactory no end culture C	M	Unsatisfactory C	M
Gram Negative								
Acinetobacter lwoffi	0	1	0	1	0	0	0	0
Citrobacter diversus	2	0	1	0	1	0	0	0
Enterobacter agglomerans	0	2	0	1	0	1	0	0
Enterobacter cloacae	5	1	3	0	1	0	1	1
Escherichia coli	7	2	4	2	3	0	0	0
Haemophilus influenzae	11	3	3	3	4	0	4	0
Haemophilus parainfluenzae	1	0	1	0	0	0	0	0
Klebsiella pneumoniae	4	3	2	2	2	1	0	0
Klebsiella sp.	2	1	0	1	1	0	1	0
Proteus mirabilis	2	1	1	0	1	0	0	1
Pseudomonas aeruginosa	1	0	1	0	0	0	0	0
Pseudomonas sp.	1	0	0	0	1	0	0	0
Serratia marcescens	2	0	2	0	0	0	0	0
Total	38	14	18	10	14	2	6	2
Gram Positive								
Staphylococcus agalactiae	1	0	1	0	0	0	0	0
Staphylococcus aureus	5	3	3	2	2	1	0	0
Streptococcus pneumoniae	11	2	4	2	3	0	4	0
Streptococcus, Group C	1	0	0	0	1	0	0	0
Streptococcus, not Group A, B, C or G	0	1	0	1	0	0	0	0
Beta Streptococcus, Group B	0	1	0	1	0	0	0	0
Beta Streptococcus, not Group A or B	1	0	1	0	0	0	0	0
Micrococcus sp.	0	1	0	1	0	0	0	0
Candida albicans	1	0	1	0	0	0	0	0
Total	20	8	10	7	6	1	4	0
Total Number of Pathogens Isolated	58	22	28	17	20	3	10	2

Table 5. Clinical and Radiographic Response
Evaluable Patients

	Cefotetan		Moxalactam	
	Clinical	Radiographic	Clinical	Radiographic
Completely Cleared	78	34	37	17
Improved	28	46	12	24
No Change	5	26	1	8
Worse	0	5	0	1

Table 6. Mean Plasma and Urine Concentrations of Cefotetan

Plasma Concentrations (µg/ml)

	1 gram	2 gram	3 gram
Pre-Dose	54.2	33.9	26.8
Post-Dose	119.0	237.7	270.7

Plasma Tautomer Levels (%)

	1 gram	2 gram	3 gram
Pre-Dose	4.9	10.2	8.6
Post-Dose	3.6	8.6	7.1

Urinary Excretion Levels (µg/ml)

1 gram	2 gram	3 gram
—	2015.3	2968.14

Urine Tautomer Levels (%)

1 gram	2 gram	3 gram
—	9.1	5.5

g. Safety

A total of 153 adverse effects (39 clinical and 60 abnormal laboratory values) were reported with cefotetan and 67 (39 clinical and 28 laboratory abnormalities) with moxalactam.

Of the 170 cefotetan-treated patients, 53 (31.2%) patients experienced one or more adverse clinical effects. Abnormal laboratory values occurred in 31 (18.2%) patients. Cefotetan was discontinued in 1 (1%) patient because of adverse clinical effects and in none of the patients because of laboratory abnormalities.

Of the 82 moxalactam-treated patients, 21 patients (25.6%) experienced one or more clinical adverse effects. Nineteen patients (23.2%) experienced abnormal laboratory values. Moxalactam was not discontinued in any patient because of adverse clinical effects or laboratory abnormalities.

A detailed enumeration of these adverse events follows in tables 7-10.

Table 7. Adverse Clinical Effects in 170 Patients Treated with Cefotetan

Type of Reaction	Total Number of Reactions	Relationship to Drug: Definite	Probable	Possible	Probably Not	Definitely Not
Local Reactions						
Discomfort	9	0	0	0	4	5
Swelling	4	0	0	0	4	0
Inflammation	1	0	0	0	0	1
Infiltration	11	0	0	0	2	9
Redness	8	0	0	0	7	1
Edema	1	0	0	0	1	0
Bruising	1	0	0	0	0	1
Induration	1	0	0	0	0	1
Phlebitis	3	0	1	1	1	0
Subtotal	39	0	1	1	19	18
Hypersensitivity						
Rash	3	0	2	0	1	0
Gastrointestinal						
Diarrhea	16	0	3	4	6	3
Nausea	7	0	1	0	3	3
Vomiting	1	0	1	0	0	0
Indigestion	1	0	0	0	1	0
Subtotal	25	0	5	4	10	6
Central Nervous System						
Headache	6	0	0	1	2	3
Dizziness	3	0	0	0	2	1
Lightheadedness	1	0	0	0	1	0
Subtotal	10	0	0	1	5	4
Miscellaneous						
Pain	7	0	0	0	1	6
Cardiovascular Accident	1	0	0	0	0	1
Sore mouth	1	0	1	0	0	0
Dry mouth	1	0	0	0	0	1
Tachycardia	1	0	0	0	1	0
Cough	1	0	0	0	0	1
Infection, eye	1	0	0	0	0	1
Hematoma	1	0	0	0	0	1
Sore throat	1	0	0	0	0	1
Parasthesia	1	0	0	0	0	1
Subtotal	16	0	1	0	2	13
Total Number of Reactions	93	0	9	6	37	41

Number of Patients with Reactions 53

Table 8 Adverse Laboratory Values in 170 Patients Treated with Cefotetan

Type of Reaction	Total Number of Reactions	Relationship to Drug				
		Definite	Probable	Possible	Probably Not	Definitely Not
Hematologic						
Eosinophils increased	3	0	2	1	0	0
Thrombocytosis	13	0	3	8	2	0
Hemoglobin decreased	4	0	0	1	2	1
Hemotocrit decreased	4	0	0	1	2	1
RBC decreased	2	0	0	0	1	1
Prothrombin Time increased	2	0	0	2	0	0
Direct Coombs test positive	2	1	0	0	1	0
Anemia	2	0	0	0	2	0
Subtotal	32	1	5	13	10	3
Hepatic						
SGOT increased	6	0	0	5	1	0
SGPT increased	7	0	2	4	1	0
LDH increased	7	0	0	5	1	1
Alk Phos increased	4	0	0	2	2	0
Subtotal	24	0	2	16	5	1
Renal						
BUN increased	1	0	0	0	1	0
Creatinine increased	1	0	0	0	0	1
Bacteriuria	1	0	0	0	0	1
Proteinuria	1	0	0	1	0	0
Subtotal	4	0	0	1	1	2
Total Number of Reactions	60	1	7	30	16	6
Number of Patients with Reactions	31					

Table 9. Adverse Clinical Effects in 81 Patients Treated with Moxalactam

Type of Reaction	Total Number of Reactions	Relationship to Drug				
		Definite	Probable	Possible	Probably Not	Definitely Not
Local Reaction						
Discomfort	4	0	0	0	4	0
Swelling	1	0	0	0	1	0
Infiltration	2	0	0	0	1	1
Redness	6	0	0	0	5	1
Edema	1	0	0	0	1	0
Subtotal	14	0	0	0	12	2
Hypersensitivity						
Itching	1	0	0	0	1	0
Rash	1	1	0	0	0	0
Rash with Itching	1	0	0	1	0	0
Subtotal	3	1	0	1	1	0
Gastrointestinal						
Diarrhea	3	0	0	0	2	1
Nausea	5	0	0	0	5	0
Vomiting	1	0	0	0	1	0
Subtotal	9	0	0	0	8	1
Central Nervous System						
Headache	1	0	0	0	0	1
Dizziness	2	0	0	1	1	0
Confusion	1	0	0	0	1	0
Agitation	1	0	0	0	1	0
Subtotal	5	0	0	1	3	1
Miscellaneous						
Pain	4	0	0	0	0	4
Cramps	2	0	0	0	2	0
Burning, Generalized	1	0	0	0	1	0
Occlusion, Artery	1	0	0	0	0	1
Subtotal	8	0	0	0	3	5
Total of Reactions	39	1	0	3	27	9
Number of Patients with Reactions	21					

Table 10. Adverse Laboratory Values in 81 Patients Treated with Moxalactam

Type of Reaction	Total Number of Reactions	Relationship to Drug				
		Definite	Probable	Possible	Probably Not	Definitely Not
ABNORMAL LABORATORY VALUES						
Hematologic						
Eosinophils increased	3	0	0	2	1	0
Monocytes increased	1	0	0	1	0	0
Thrombocytsis	7	0	3	4	0	0
Prothrombin Time increased	4	0	1	3	0	0
Direct Coombs Test positive	4	0	2	1	1	0
Subtotal	19	0	6	11	2	0
Hepatic						
SGOT increased	2	0	1	0	1	0
SGPT increased	2	0	1	0	1	0
LDH increased	1	0	0	0	1	0
Alk Phos increased	2	0	1	0	1	0
Subtotal	7	0	3	0	4	0
Renal						
Albuminuria	1	0	0	0	1	0
Proteinuria	1	0	0	1	0	0
Subtotal	2	0	0	1	1	0
Total Number of Reactions	28	0	9	12	7	0
Number of Patients with Reactions	19					

h. Conclusions

Efficacy: Of the 111 evaluable patients treated with cefotetan, 86% (75/87) had a satisfactory bacteriologic response resulting in the eradication of the initial pathogen, and another 24 patients had a presumed satisfactory response because there was no appropriate culture material due to clinical improvement. Therefore, a satisfactory response was documented or presumed in 99/111 patients (89%). Of the evaluable moxalactam patients 95% (36/38) had a satisfactory bacteriologic response and 12 had a presumed satisfactory response. Therefore, a satisfactory response was documented or presumed in 48/50 patients (96%).

Complete clearing or substantial improvement in clinical signs or symptoms occurred in 95% of cefotetan patients, compared with 98% of the moxalactam patients. High and prolonged plasma levels and high urinary concentrations of cefotetan were obtained with 2 and 3 gram doses.

Safety: The safety and tolerance of both drugs were not significantly different.

Overall: Intravenous cefotetan, 2 or 3 grams every 12 hours, appears to be as safe and effective as moxalactam, 1 or 2 grams every 8 hours, in treating lower respiratory tract infections due to susceptible pathogens and it produces high and prolonged plasma levels and urinary concentration of drug.

C. Skin and Skin Structure Infection Controlled Studies

1. Protocol 2-2-3-01. A multicenter comparative study of cefotetan and cefotaxime in the treatment of hospitalized patients with skin and skin-structure infections.

a. Investigators

Michael A. Castellano, M.D.	New York, NY
Ronald W. Geckler, M.D.	Baltimore, M.D.
Stephen R. Zellner, M.D.	Ft. Myers, FL
Thomas Nolen, M.D.	Alabaster, AL
Peter [illegible]. Gross, M.D.	Hackensack, NJ
Paul Jurgensen, M.D.	Savannah, GA

b. Design of the Study

Prior to initiation of the study, the appropriate institutional review committees approved the study protocol.

Hospitalized adult patients with bacterial skin and skin-structure infections, likely to be susceptible to cephalosporin-type antibiotics, and who were considered likely to meet all criteria for entry into the study were selected.

All investigators used the same protocol. Written informed consent was obtained from each patient.

All infections were to be confirmed by appropriate clinical findings and isolation and identification of pathogen(s) to genus and species from appropriate cultures obtained prior to intitation of study drug therapy. The pathogen(s) were to be susceptible to the study drug by disk testing using the Kirby-Bauer method and/or MIC determination.

A predetermined randomization schedule was provided for each investigator by the Clinical Research Department of Stuart Pharmaceuticals. According to the randomization, patients selected for the study were assigned to treatment with either cefotetan or cefotaxime. Twice as many patients were assigned to cefotetan as cefotaxime.

Treatment with cefotetan and cefotaxime was by the intravenous route. Cefotetan was administered every 12 hours and cefotaxime every 6 hours. For both drugs, the individual dose was 1 or 2 grams depending on the severity of the infection and the patient's condition. The duration of treatment was to be for a minimum of five days. No antimicrobials, other than the study drug, were to be given.

Treatment with the study drug could begin before results of bacteriologic studies were known; however, when these results became available, if no pathogen was isolated or if the pathogen was resistant to the study drug, treatment was to be discontinued.

Specific entry and withdrawal criteria were basically identical to the previously reviewed protocols, except that patients had to have skin and skin structure infections.

Evaluability and Efficacy Criteria

Criteria for Evaluable Cases

1. There were appropriate pretherapy clinical findings of skin or soft tissue infection.

2. A pre-therapy culture of the site was obtained before starting the study drug.

3. A specific pathogen(s) was isolated and identified from the pre-therapy culture.

4. In vitro microbiologic testing did not indicate that the pathogen(s) was resistant to the study drug.

5. If the infection had previously been treated with an antimicrobial, that drug was discontinued before obtaining the pre-therapy culture, and there was documentation that the previous treatment had been unsuccessful.

6. A during-therapy and end of therapy culture were obtained if there was culture material available.

7. The predetermined random schedule of drug assignment was followed.

8. The study drug had been administerd long enough to allow a judgment as to its effect or lack of effect (minimum of 48 hours).

9. No antimicrobial, other than the study drug, had been administered from the time of pre-therapy culture until the end of therapy culture was obtained.

10. No underlying condition or disease obscured or prevented evaluation of the patients response to study drug treatment.

Clinical Response

The patient's clinical response to treatment was judged as either satisfactory or unsatisfactory according to the following definitions:

Satisfactory

The clinical response was considered satisfactory if local and systemic signs of the infection disappeared or substantially improved with treatment.

In the event of a patient's death: If the patient died of an underlying disease but the infection had clinically disappeared or substantially improved, the clinical response was considered satisfactory.

Unsatisfactory

The clinical response was considered unsatisfactory if there was clinical persistence or worsening of the local and systemic signs or symptoms of infection.

Bacteriologic Response

The bacteriologic response to treatment was judged as either satisfactory or unsatisfactory according to the following definitions:

Satisfactory

The bacteriologic response was considered satisfactory if, on end of treatment culture, the causative pathogen(s) had been eradicated. The response was also considered satisfactory if the causative pathogen(s) had been eradicated and a new pathogen was present but without clinical evidence of a new infection.

The bacteriologic response was presumed satisfactory in infections where the eradication of the infection has resulted in no material being available for culture; e.g., in the case of a soft tissue infection in which the lesion has healed.

Unsatisfactory

The bacteriologic response was considered unsatisfactory if, on post treatment culture, the causative pathogen(s) had not been eradicated.

c. Evaluable Patients

Table 1. Distribution of Patient Evaluability by Investigator

	Cefotetan		Cefotaxime	
Investigators	Evaluable	Non-Evaluable	Evaluable	Non-Evaluable
Castellano	9 (60%)	6 (40%)	6 (67%)	3 (33%)
Geckler	8 (62%)	5 (38%)	4 (80%)	1 (20%)
Gross	2 (67%)	1 (33%)	0 (0%)	0 (0%)
Jurgensen	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Nolen	5 (56%)	4 (44%)	4 (100%)	0 (0%)
Zellner	3 (100%)	0 (0%)	1 (100%)	0 (0%)
Total	28 (64%)	16 (36%)	15 (79%)	4 (21%)

d. Patient Characteristics

All patients were hospitalized. For both treatment gruops, the populations tended to older aged, mean age 61.1 for cefotetan patients, and 62.2 for cefotaxime patients. The two drug groups were balanced as far as sex distribution is concerned (57% male in the cefotetan group and 53% male in the cefotaxmine group).

Most patients were in good or fair general condition at the time of entry into the study. The status of renal function as clinically judged by the investigator, was reported to be normal in 89% of the cefotetan patients and 95% of the cefotaxime patients. One or more significant underlying diseases were present in most patient. Most frequent were cardiovascular disease and diabetes mellitus.

e. Reasons for excluding non-evaluable cases

Twenty paients were not evaluable for efficacy analysis for the following reasons: 12 because there was no pathogen isolated from the prestudy cultures, 5 patients because the organism isolated was resistant to the study drug, one because there was no follow-up culture, one because the treatment schedule was not followed and one because treatment was less than 48 hours.

f. The following tables 2 and 3 represent the sponsor's efficacy summary. This reviewer found the following additional patients unevaluable for efficacy and they have been excluded from the overall summary at the conclusion of this NDA review.

Page No.	Patient No.	Drug	Reason for Non-Evaluability
228	2	CTN	Surgical intervention
230	21	CTN	Less than five days treatment
230	28	CTN	Less than five days treatment
231	8	CTX	Sensitivities not obtained
232	14	CTX	Less than five days treatment
234	3	CTN	Sensitivities not obtained
236	1	CTN	Sensitivities not obtained
238	2	CTN	Sensitivities not obtained
238	3	CTX	Resistant to CTN

In addition, the following changes were made.

Page No.	Patient No.	Drug	Changes made
238	1	CTN	S. aureus deleted
238	4	CTN	E. coli added

Most infections for both the cefotetan group and the cefotaxime group were cellulitis in 16 patients and in 12 patients, respectively. The other types of infections included wound infections, abscesses and ulcer infections.

Table 2

Pathogen Isolated	Number of Patients	Bacteriologic Response		Clinical Response		
		Satisfactory	Unsatisfactory	Completely Cleared	Improved	Unchcharged
Cefotetan						
Staphylococcus aureus	11	11	0	9	2	0
Streptococcus agalactiae	2	2	0	1	1	0
Streptococcus pyogenes	1	1	0	0	1	0
Bacteroides sp.	1	1	0	1	0	0
Enterobacter cloacae	1	1	0	0	1	0
Polymicrobial	11	9	2	7	4	0
TOTAL	28	26	2	18	10	0
Cefotaxime						
Staphylococcus aureus	3	3	0	3	0	0
Staphylococcus epidermidis	1	1	0	1	0	0
Streptococcus, Group C	1	1	0	1	0	0
Aeromonas hydrophilia	1	1	0	1	0	0
Proteus mirabilis	2	2	0	1	1	0
Proteus vulgaris	1	1	0	0	1	0
Pseudomonas aeruginosa	1	1	0	0	1	0
Polymicrobial	5	3	2	2	2	1
TOTAL	15	13	2	9	5	1

Table 3

Polymicrobial Organism	Bacteriologic Response		Clinical Response		
	Satisfactory	Unsatisfactory	Completely Cleared	Improved	Unchchanged
Cefotetan					
Staphylococcus aureus	5	1	4	2	0
Streptococcus epidermidis	2	1	2	1	0
Streptococcus agalactiae	1	0	1	0	0
Streptococcus pyogenes	1	0	1	0	0
Streptococcus, Group G	1	0	0	1	0
Bacteroides fragilis	0	1	0	1	0
Enterobacter cloacae	1	0	0	1	0
Escherichia coli	2	2	1	3	0
Proteus mirabilis	4	1	4	1	0
Pseudomonas maltophilia	1	0	1	0	0
Salmonella enteritidis	1	0	1	0	0
Serratia marcescens	0	1	0	1	0
Cefotaxime					
Staphylococcus aureus	1	1	0	2	0
Staphylococcus epidermidis	1	0	1	0	0
Streptococcus, sp	1	0	1	0	0
Streptococcus, Group C	1	0	0	1	0
Streptococcus, not Group A	1	0	1	0	0
Streptococcus, alpha-hem	1	0	1	0	0
Streptococcus sp.	1	0	1	0	0
Diptheroids	1	0	1	0	0
Enterobacter cloacae	0	1	0	1	0
Escherichia coli	0	1	0	0	1
Klebsiella oxytoca	0	1	0	0	1
Proteus vulgaris	0	1	0	0	1

g. Safety

A total of 21 adverse effects (8 clinical effects and 13 abnormal laboratory values) were reported with cefotetan, and 19 (6 clinical and 13 laboratory) with cefotaxime.

Of the 44 cases treated with cefotetan 30 (68%) did not have an adverse experience, and 10 (53%) of the 19 cases treated with cefotaxime did not have an adverse experience.

The laboratory abnormalities were minor and there were no statistical differences between cefotetan and cefotaxime.

The only clinical reaction felt to be probably drug related was one patient treated with cefotaxime who developed diarrhea.

h. Conclusions

None of the individual investigators studied a large enough number of patients for any valid statistical comparison to be made.

Of total evaluable patients, 26/28 (93%) cefotetan treated infections were bacteriologically eradicated, and 13/15 (87%) of cefotaxime treated infections were eradicated. In this small number of patients cefotetan appears to be as safe and effective as cefotaxime in the treatment of skin and skin structure infections caused by susceptible pathogens.

D. OB-GYN Infection-Controlled Studies

1. Protocol 2-4-2-01. A multicenter comparative study of intravenous cefotetan and Moxam (moxalactam disodium, Lilly) in gynecological infections.

a. Investigators

R. David Miller, M.D.
Edward R. Newton, M.D.
Alfred N. Poindexter, III, M.D.

b. Study Design

This is a multicenter open, comparative, randomized study designed to evaluate the therapeutic effectiveness and safety of a q12h dosing regimen of cefotetan as compared to a q8h or q12h dosing regimen of moxalactam disodium in the treatment of obstetric and gynecological infections and skin/skin structure infections. The information submitted was a preliminary report on an ongoing study.

Number of Patients

Fifty-three patients were enrolled in the study at the time of this report of which 19 (17 gynecological and 2 skin/skin structure) patients were evaluable for efficacy. All 53 patients were evaluated for safety.

Test Drug Schedule

According to the randomization schedule, patients were assigned to the study drug treatments on a 2:1 ratio (cefotetan:moxalactam). Patients recevied either cefotetan 2 gm, q12h by IV infusion for 5 to 10 days or moxalactam 2 gm, q8h or 12 h by IV infusion for 5 to 10 days. The mean duration of therapy for all evaluable patients was 5.6 days for cefotetan and 4.9 days for moxalactam.

c. Results

See Table 1 for the bacteriological results for the OB-GYN infections treated as of the date of the report of this study according to the sponsor's evaluation.

This reviewer additionally found 5 of the 11 cefotetan treated patients unevaluable and 3 of the 5 moxalactam treated patients. The reasons for the non-evaluability follow.

Page No.	Patient No.	Drug	Reason for Non-Evaluability
247	2	MOX	Sensitivities not obtained
247	3	CTN	Sensitivities not obtained
247	13	CTN	No pathogen isolated pre-Rx and no sensitivities
247	15	CTN	Sensitivities not obtained
248	17	CTN	Sensitivities not obtained
249	8	MOX	Less than five days treatment
249	12	MOX	Less than five days treatment
249	15	CTN	Less than five days treatment

In addition the following changes were made.

Page No.	Patient No.	Drug	Changes made
247	12	CTN	B. bivius and B. melaninogenicus deleted

In the 2 evaluable skin/skin structure patients (1 cefotetan and 1 moxalactam), both patients had clearing of their

surgical wound infections, and in both patients the bacteriological response was presumed satisfactory.

Overall, both drugs were well tolerated, with similar types of non-serious adverse effects occurring with both drugs.

d. Conclusion

The data reviewed was from a preliminary report of an ongoing multicenter comparative study. These data indicate that cefotetan was being well tolerated and that it compared favorably with moxalactam as therapy for the treatment of obstetrical and gynecological infections.

E. Intra-abdominal Infections-Controlled Studies

1. Protocol 2-3-2-01. multicenter comparative study of intravenous cefotetan and Moxam (moxalactam disodium, Lilly) in the treatment of hospitalized patients with intra-abdominal infections.

a. Investigators

John A. Boswick, Jr., M.D., FACS
Joseph G. Jemsek, M.D.
Ronald T. Lewis, M.D., B.S., M.Sc., FRCS(C), Gia That Ton, M.D.

b. Study Design

This is a multicenter, open, comparative, randomized study designed to evaluate the therapeutic effectiveness and safety

of a q12h dosing regimen of cefotetan as compared to a q8h or q12h dosing regimen of moxalactam disodium in the treatment of intra-abdominal infections and skin/skin structure infections. The information submitted was a preliminary report on an ongoing study.

Number of Patients

Eighteen patients were enrolled in the study at the time of this report. Of those, 10 patients (6 intra-abdominal and skin/skin structure) were evaluable for efficacy. All 18 patients were evaluated for safety.

Test Drug Schedule

According to the randomization schedule, patients were assigned to the study drug treatments on a 2:1 ratio (cefotetan:moxalactam). Patients received either cefotetan 2 gm, q12h by IV infusion for 5 to 10 days or moxalactam 2 gm, q8h or q12h by IV infusion for 5 to 10 days. The mean duration of therapy for all evaluable patients was 6.5 days for both drugs.

c. Results

See Table 1 for the bacteriological results for the intra-abdominal infections treated as of the date of the report of this study according to the sponsor's evaluation.

This reviewer also disqualified the following additional patients.

Page No.	Patient No.	Drug	Changes made
260	4	CTN	Less than five days treatment
260	7	CTN	Clinical diagnosis not acceptable

Four of the 4 evaluable skin and skin structure infections were cured by cefotetan.

Overall, both drugs were well tolerated. There was one moxalactam-treated patient that experienced a significant increased prothrombin time that required discontinuation of treatment.

d. Conclusion

The data reviewed was from a preliminary report of an ongoing multicenter comparative study. These data indicate that cefotetan was being well tolerated and that it compared favorably with moxalactam as single-agent therapy in the treatment of intra-abdominal infections.

Table 1. Bacteriological Response Related To Pathogens
Gynecological Patients

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response: Satisfactory	Presumed Satisfactory	Unsatisfactory
Cefotetan	F. Mortiferum, Varium	1	1	0	0
	N. Gonorrhoeae	7	7	0	0
	Anaerobes NOS	1	1	0	0
	Polymicrobial	2	2	0	0
	Total	11	11 (100%)	0 (0%)	0 (0%)
Moxalactam	N. Gonorrhoeae	3	3	0	0
	E. Coli	1	1	0	0
	Polymicrobial	2	1	1	0
	Total	6	5 (83%)	1 (17%)	0 (0%)

Table 2. Bacteriological Response Related to Pathogens
Evaluable Intra-Abdominal Patients

Treatment	Pathogens	Number of Evaluable Cases	Bacteriological Response: Satisfactory	Presumed Satisfactory	Presumed Unsatisfactory
Cefotetan	Polymicrobial	3	0	3	0
	Total	3	0	3 (100%)	0
Moxalactam	Proteus [illegible]abilis	1	0	0	1
	Strep. alpha-hemolytic	1	0	1	0
	Polymicrobial	1	0	1	0
	Total	3	0	2 (67%)	1 (33%)

F. Prophylaris - Controlled Studies

The sponsor has submitted the results of the following controlled studies.

1. Transurethral surgery - 3 investigators
   258 evaluable patients - 124 cefotetan, 134 cefotaxime

2. Cesarean section - 6 investigators
   215 evaluable patients - 142 cefotetan, 73 cefoxitin

3. Hysterectomy - 5 investigators
   132 evaluable patients - 87 cefotetan, 45 cefoxitin

4. Colorectal surgery - 3 investigators
   40 evaluable patients - 26 cefotetan, 14 cefoxitin

5. Biliary tract surgery - 2 investigators
   20 evaluable patients - 16 cefotetan, 4 cefoxitin

6. Appendical surgery - 3 investigators
   7 evaluable patients - 4 cefotetan, 3 cefoxitin

7. Upper GI surgery - 1 investigator
   5 evaluable patients - 4 cefotetan , 1 cefoxitin

United Kingdom Studies

8. Colorectal surgery - vs. metronidazole
9. Transurethral - vs. gentamicin
10. Appendical - vs. metronidazold
11. Acute abdominal - vs. gentamicin and tinidazole
12. Biliary tract - vs. cefazolin

No United States approved claim for comparative drug (8 - 11)

Comment

The criteria for evaluability in the United States studies submitted are more strict than in previous prophylaxis studies reviewed by this reviewer. Infections were actively looked for, including bacteriologic cultures, even in patients who were asymptomatic and afebrile. Additionally, a urine colony count of 10^4 or more organisms in a clean voided specimen was considered an infection and therefore a failure. These criteria explain the somewhat higher infection rates in these studies.

However, the infection rates following either cefotetan prophlaxis or prophylaxis with the comparative antibiotics, were similar.

A. Evaluable Studies

1. Transurethral Surgery

Protocol Title: Multicenter, Randomized Open, Comparative Study of Intravenous Cefotetan and Claforan (cefotaxime sodium) as Prophylactic Agents in Transurethral Surgery

a. Investigators

Clair E. Cox, M.D.
Paul O. Madsen, M.D.
W. Glen Wells, M.D.

b. Study Design

This multicenter, controlled, randomized study compared intravenous cefotetan administered once before surgery with cefotaxime administered once before surgery, once during surgery, and once within 2 hours after surgery. Most patients were males, undergoing transurethral surgery of the prostate or bladder. Urine cultures were obtained within 48 hours before surgery, 24 hours after surgery, 48-96 hours after surgery and at the time of hospital discharge.

c. Criteria for Evaluability

1. There were no pre-therapy clinical findings suggestive of infection.

2. A pre-therapy quantitative urine culture was obtained within 48 hours before starting the study drug. The quantitative urine bacterial count had to be less than 10,000 organisms per ml of urine in a clean voided specimen or no growth of bacteria in a catheter sample.

3. If a patient had been treated with an antimicrobial drug, that drug had to be discontinued 1 week before obtaining the pre-therapy quantitative culture.

4. Post-surgical quantitative urine cultures were obtained.

5. The predetermined randomization schedule of drug assignment was followed.

6. The study drug had been administered according to the schedule in the protocol.

7. No antimicrobial, other than the study drug, had been administered from the time of pre-therapy quantitative urine culture until the final evaluation, prior to discharge.

8. No underlying condition or disease obscured or prevented evaluation of the patient's response to study drug treatment.

Efficacy Evaluation

Clinical Response

The patient's clinical response to the prophylactic course of treatment was assessed as either a success, failure or unevaluable according to the following definitions.

Success

The clinical response was considered successful if the patient did not develop clinical signs or symptoms of infection prior to the predischarge evaluation.

Failure

The clinical response was considered a failure if the patient developed the clinical signs and symptoms of an infectious process which necessitated the need for therapeutic measures [i.e., antibiotics(s)]. Patients with febrile morbidity were also considered failures. Febrile morbidity was defined as: Oral temperature 100. 4°F (38°C) on any 2 of the first 7 postoperative days, excluding the first 24 postoperative hours.

Unable to Evaluate

Evaluation could not be made if the patient was prematurely lost to study because of voluntary withdrawal or relocation of residence.

Bacteriologic Response

Bacteriologic response was assessed on the basis of quantitative urine cultures which were obtained: 1) from the Foley catheter 1 day after surgery; 2) prior to removal of the Foley catheter, 2 to 4 days after surgery; 3) from the first voided specimen after removal of the Foley catheter; and 4) prior to hospital discharge. Some patients also had quantitative cultures 7 to 14 days after hospital discharge, if required.

According to these criteria, the endpoints for bacteriological response were:

Satisfactory; No growth in a catheter specimen or less than 10,000 organisms per ml in a non-catheter specimen in any of the post-treatment urine cultures.

Unsatisfactory: Any growth of pathogens(s) from a catheter specimen or 10,000 or more organisms per ml in a non-catheter specimen in any of the post-treatment urine culture.

Unable to Evaluate: No evaluation of the bacteriologic response could be made.

d. Number of Patients

Three hundred and twenty nine patients were entered into the study, and 258 were evaluable for efficacy analysis (124 cefotetan-treated, 134 cefotaxime-treated).

Table 1 . Patient Evaluability by Investigator

Transurethral Surgery

Investigator	Total Number	Randomized Study Drug					
		Cefotetan			Cefotaxime		
		Evaluable	Non-Evaluable	Total	Evaluable	Non-Evaluable	Total
Dr. Cox	121	50	13	63	50	8	58
Dr. Madsen	127	42	21	63	49	15	64
Dr. Wells	81	32	8	40	35	6	41
OTAL	329	124(75%)	42 (25%)	166	134 (82%)	29 (18%)	163

e. Test Drug Schedule

The cefotetan-treated patients received a single dose of 2gm administered intravenously, 30 to 60 minutes before surgery. Cefotaxime-treated patients received 1gm 30 to 120 minutes after the first dose and 1gm given within 2 hours after surgery. Within each center, patients were randomized to cefotetan or cefotaxime in a 1:1 ratio.

f. Results

Efficacy

The clinical course of patients given prophylaxis was unsatisfactory in 8% of patients given cefotetan and in 7% of patients given cefotaxime. Bacteriologically demonstrated infections as defined by the protocol were seen in 8% of patients given cefotetan prophylaxis and in 6% of the patients given cefotaxime.

Safety

Intravenous cefotetan was well-tolerated. No drug-related adverse signs or symptoms were reported in the cefotetan-treated patients. Two reports of diarrhea and 1 report of a rash were considered drug-related in the cefotaxime-treated patients.

The following tables and comments delinated in more detail the results of the study.

Table 2. Typed and Duration of Procedures

Transurethral Surgery

	Evaluable Randomized Drug		Non-Evaluable Randomized Drug	
	Cefotetan N=124	Cefotaxime N=134	Cefotetan N=42	Cefotaxime N=29
Surgical Procedure				
Transurethral Resection, Prostate (TURP)	45	52	12	7
Transurethral Resection, Bladder (TURB)	13	18	3	1
Biopsy of Prostate	4	5	0	1
Multiple Procedures	35	39	10	6
Biopsy of Bladder	4	4	1	0
Ureteral Stonebasket	2	2	0	1
Urethrotomy	2	0	1	0
Cystoscopy	3	0	0	0
Excision of Urethral Polyp	1	0	1	0
Fulguration of Bladder Tumor	1	1	0	0
Ureterolithotomy	1	2	0	1
TURP & TURB	0	0	0	1
Cauterization	1	0	0	0
Cystoscopy/Bladder Biopsy	5	6	2	2
Incision of Bladder Neck	1	0	0	0
Incision of Prostate	0	2	0	0
Transurethral Cauterization and Trigone	4	2	1	2
Transurethral Fulguration of Prostate	1	0	0	0
None	0	0	11	6
Frequency of Dosing/Grams per Dose				
Once/1	0	0	1	2
Once/2	124	0	31	1
Twice/1	0	0	0	1
Three/1	0	134	0	20
None/0	0	0	10	5
Duration of Surgery (minutes)[1]				
Mean	37.5	43.5	55.5	55.4
Median	35.0	35.0	40.1	31.0
Range	5-135	5-160	10-215	10-270
Duration of Post-surgery Hospitalization Stay (days)[1]				
Mean	5.5	5.4	5.5	5.8
Median	4.0	5.0	5.0	5.0
Range	2-39	2-36	2-13	1-12

[1]Using patients where surgery was performed

The reason for clinical failures among the evaluable cases were the following.

Reason	Number of Patients	
	Cefotetan	Cefotaxime
Urinary Tract Infection	8	4
Febrile Morbidity	2	1
Urinary Tract Infection and Febrile Morbidity	0	1
Clinical Infections	0	2
Epididymitis	0	1
TOTAL	10	9

Bacteriological Results

Of the 258 evaluable patients, 97 (78%) of the cefotetan-treated and 111 (83%) of the cefotaxime-treated patients had no growth in their pre-therapy quantitative urine cultures. Twenty six (21%) of the cefotetan group and 21 (16%) of the cefotaxime group were reported as either having normal flora or the isolation of a contaminant in the pre-therapy urine cultures.

There were 15 patients, 9 cefotetan and 6 cefotaxime or treated who had unsatisfactory bacteriological outcomes.

In the cefotetan-treate patients, no polymicrobial infections were reported in the urine cultures from the bacteriologicallyunsuccessful group. Eight of the nine single pathogens isolated identified and sensitivity tested were Gram positive, while one was Gram nagative. All of the pathogens isolated were resistant to cefotetan except the Staphylococcal sp., which was not tested.

Polymicrobial infections were reported in 4 of the cefotaxime-treated patients with bacteriologically unsatisfactory responses. In these 4 cases, both Gram positive organisms isolated were resistant to cefotaxime. Enterobacter cloacae was sensitive to cefotaxime, while sensitivities were not carried out on the Pseudomonas sp. and the Gram negative rods. In the 2 remaining cefotaxime patients, single pathogens were isolated and both were Gram negative. Pseudomonas aeruginosa was resistant to cefotaxime while Proteus mirabilis was sensitive.

Bacteriologic response to treatment could not be evaluated in 3 patients, 1 cefotetan and 2 cefotaxime-treated. The 1 cefotetan-treated patient had a successful clinical response and follow-up urine cultures were not obtained. In the cefotaxime group, 1 patient was a clinical failure, while urine cultures demonstrated no growth; the other patient was also a clinical failure and follow-up cultures were not obtained.

The specific pathogens isolated in the bacteriologically unsatisfactory evaluable cases are listed in the following Table 2.

	Number of Patients	
	Cefotetan	Cefotaxime
Number of Failures	9	6
Pathogens		
Polymicrobial		
S. epidermidis coag neg. and *Pseudomonas sp.*	0	2
Str. faecalis and *Ent. cloacae*	0	1
Str. faecalis and gram negative rods	0	1
Single		
Gram Positive		
Str. faecalis	5	0
Enterococcus	1	0
Staphylococcus sp.	1	0
S. epidermidis, coag. neg.	1	0
Gram Negative		
Ps. aeruginosa	1	1
P. mirabilis	0	1

Conclusions

One 2gm dose of cefotetan, administered intravenously before transurethral surgery, was as safe and effective as three 1gm doses of cefotaxime, in preventing postoperative urinary tract and other infections. Cefotaxime has an approved prophylaxis claim for use in genitourinary tract surgery.

2. Cesarean Section

Protocol Title:

MULTICENTER, OPEN, COMPARATIVE STUDY OF INTRAVENOUS CEFOTETAN AND MEFOXIN® (cefoxitin sodium) AS PROPHYLACTIC AGENTS IN CESAREAN SECTIONS

a. Investigators:

	Sites:
B. Benigno, M.D.	Atlanta, GA
G. Cunningham, M.D.	Dallas, TX
J. Elliott, M.D.	Phoenix, AZ
R. Galask, M.D.	Iowa City, IA
E. Makowski, M.D.	Denver, CO
A. Poindexter, M.D.	Houston, TX

b. Study Design:

This was a multicenter, open, randomized investigation that compared the prophylactic effectiveness and safety of cefotetan with cefoxitin. All female patients were hospitalized and were scheduled to undergo primary cesarean section or repeat cesarean surgery.

Twenty-four hours prior to surgery, urine cultures were obtained. Patients who presented with ruptured membranes prior to surgery were to have a uterocervical specimen obtained for culture. All aerobic and anaerobic potential pathogens were to be isolated, identified and sensitivity tested.

During surgery a culture of the endocervical area, via an intra-abdominal approach was obtained after the baby and placenta were delivered. In addition, a culture was obtained from the surgical wound at closure.

Post-operative urine cultures were obtained within 24 hours. Further cultures were obtained, when infection was apparent, from those sites where infection was to be expected to occur (wound site, endometrium, urine and blood). All pathogens(s) isolated were tested. Finally, plasma was obtained from the cefotetan-treated patients to assay for cefotetan levels.

c. Criteria for Evaluability

The criteria for evaluability for this protocol were similar to those for the Transurethral Surgery Protocol, with the following modifications.

1. The pre-therapy quantitative urine and endocervical cultures (when membranes were ruptured) were obtained, when possible, within 24 hours before starting the study drug.

2. The pre-therapy quantitative urine bacterial count had to be less than 100,000 organisms per ml of urine in a Foley catheter specimen.

3. Previous antimicrobials had been discontinued two weeks prior to therapy, and no concomitant antimicrobials had been administered from the time of pre-therapy cultures until the patient's scheduled follow-up study evaluation visit.

Efficacy Evaluation

Clinical Response

The patient's clinical response to the prophylactic course of treatment was to be assessed as either a success, a failure or unevaluable, according to the following definitions:

Success

The clinical response was to be considered successful if the patient did not develop clinical signs or symptoms of infection within the postoperative period, up to the patient's scheduled follow-up study evaluation visit.

Failure

The clinical response was considered a failure if the patient developed the clinical signs and symptoms of an infectious process which necessitated the need for therapeutic measures, such as antibiotic(s) and/or surgical intervention. Febrile morbidity was defined as: Oral temperature of 100.4°F (38°C) or greater on any 2 of the first 10 postoperative days, excluding the first 24 postoperative hours.

The clinical response was considered a failure if the patient developed one or more of the following conditions.

1. Wound Infection: 1) purulent wound drainage; 2) open wound, but no purulent drainage; 3) abnormally erythematous wound; 4) suture line abscess; 5) abnormal indurations; 6) wound hematoma.

2. Parametritis/Pelvic Cellulitis: fever, pain in lower abdomen, phlegmonous vaginal induration on examination.

3. Endometritis: fever, tenderness on pelvic examination, abnormal discharge from cervix.

4. Pelvic Abscess: documented by laparoscopy, ultrasonography, operation, or needle aspiration through the cul-de-sac.

5. Septic pelvic thrombophlebitis: Fever, pain in lower abdomen, syndrome resolved by heparin and antibiotics or documented pulmonary emboli in a patient with sepsis.

In the event of a patient's death: if the patient died as the result of a postoperative infection or died of an infection primarily, although the infection was contributory, the clinical response was considered a failure.

Unable to Evaluate

No evaluation of the clinical response could be made.

Bacteriologic response

Bacteriologic response was assessed on the basis of the following culture results:

1. quantitative urine culture one day after surgery

2. culture(s) from infected sites(s) during hospitalization.

3. culture(s) from infected site(s) 7 to 10 days after hospital discharge.

According to these criteria, bacteriologic responses were defined as:

Satisfactory: The bacteriologic response was considered satisfactory, if on all appropriate post-surgical cultures, no evidence of bacteriologic pathogen(s) was found and no infection developed.

Unsatisfactory: The bacteriologic response was considered unsatisfactory if there were 100,000 or more organisms/ml in a quantitative urine culture with or without fever. The bacteriologic response was also considered unsatisfactory if two consecutive blood cultures were positive in a patient with sepsis.

Unable to Evaluate

No evaluation of the bacteriologic response could be made.

d. Number of Patients

Two hundred and forty-eight patients were enrolled in the study; all were evaluated for safety. Two hundred and fifteen

patients were evaluable for efficacy (142 randomized to cefotetan, 73 randomized to cefoxitin).

The patient evaluability by investigator is shown in the following Table 1.

Table 1. Patient Evaluability by Investigator

Cesarean Section

Investigator	Total Number	Randomized Study Drug: Cefotetan Evaluable	Cefotetan Non-Evaluable	Cefotetan Total	Cefoxitin Evaluable	Cefoxitin Non-Evaluable	Cefoxitin Total
Dr. Benigno	32	21	0	21	10	1	11
Dr. Cunningham	66	36	7	45	19	2	21
Dr. Elliott	34	19	3	22	10	2	12
Dr. Galask	36	20	4	24	9	3	12
Dr. Makowski	50	27	5	32	16	2	18
Dr. Poindexter	30	19	1	20	9	1	10
TOTAL	248	142 (87%)	22 (13%)	164	73 (87%)	11 (13%)	84

e. Test Drug Schedule

According to the randomization schedule, within each center, patients were randomized to either cefotetan or cefoxitin in a 2:1 ratio. The cefotetan-treated patients received one 2 gm dose administered IV, immediately following clamping of the umbilical cord. The cefoxitin-treated patients received a first dose of 2 gm administered IV immediately following clamping of the umbilical cord. A second dose of 2 gm IV, 8 hours after the first dose. Subsequent doses of 2 gm IV were given every 6 hours for no more than 24 hours. For evaluable patients, no less than 3 doses and no more than 5 doses of cefoxitin were administered.

f. Results

Efficacy

The clinical course of patients given prophylaxis was unsatisfactory in 16% of the patients given cefotetan and in 14% of the patients given cefoxitin. Bacteriologically demonstrated infections were seen in 15% of the patients given cefotetan prophylaxis and 14% of the patients given cefoxitin.

Safety

Intravenous cefotetan for prophylaxis therapy was well-tolerated. Hives in a cefotetan-treated patient and pruritus in a cefoxitin-treated patient were the only drug-related adverse signs and sysmptoms reported.

The following tables and comments delineate in more detail the results of the study.

Table 2. Type and Duration of Procedures
Cesarean Section

	Evaluable		Non-Evaluable	
	Randomized Drug		Randomized Drug	
	Cefotetan N=142	Cefoxitin N=73	Cefotetan N=22	Cefoxitin N=11
Surgical Procedure				
Cesarean Section, Bilateral Tubal Ligation	48	11	7	3
Cesarean Section	45	33	7	3
Cesarean, High Transverse	0	0	1	0
Cesarean, Low Transverse	45	23	4	3
Multiple Procedures	4	6	1	1
None	0	0	2	1
Number of Doses/Grams per Dose				
One/2	142	0	19	0
Three/2	0	54	0	5
Four/2	0	1	0	1
Five/2	0	18	0	4
None/0	0	0	3	1
Duration of Surgery (minutes)[1]				
Mean	49.9	51.9	54.4	51.3
Median	45.5	50.0	50.0	49.5
Range	15-133	20-101	24-130	16-105
Duration of Post-surgery Hospitalization Stay (days)[1]				
Mean	5.5	5.6	6.9	6.1
Median	5.0	5.0	6.0	6.0
Range	3-14	4-9	4-14	4-8
Maximum Temperature (°F) Increase from Pre-Treatment to Discharge Evaluation[2]				
Number	141	73	18	10
Mean	1.6	1.8	1.8	1.7
Median	1.6	1.7	1.5	1.8
Range	-1.4 to 5.4	-0.5 to 4.6	0.0 to 3.7	-0.2 to 3.6
Worst Wound Grade				
0	128 (90%)	64 (88%)	16 (94%)	9 (90%)
1	14 (10%)	9 (12%)	1 (6%)	1 (10%)

[1]Using patients where surgery was performed

[2]A negative number indicates change was a decrease in temperature

The reasons for clinical failures among the evaluable cases were the following.

Table 3. Reasons for Clinical Failures Among Evaluable Cases

Cesarean Section Surgery

Reason	Number of Patients	
	Cefotetan	Cefoxitin
Endometritis	10	2
Endometritis/Febrile Morbidity	7	2
Endometritis/Wound Infection/ Febrile Morbidity	1	0
Urinary Tract Infection	0	2
Urinary Tract Infection/Febrile Morbidity	1	0
Wound Infection	2	3
Wound Infection/Febrile Morbidity	0	1
Febrile Morbidity	2	0
TOTALS	23	10

Bacteriological Results

Of the 215 evaluable patients, 13 (15%) of the cefotetan-treated and 5 (14%) of the cefoxitin-treated patients had unsatisfactory bacteriologic responses.

Three cefotetan and 2 cefoxitin-treated patients had single pathogens isolated.

In the cefotetan group, Enterococcus was isolated from 2 patients while G. vaginalis was isolated from 1 patient. An enterococcus and G. vaginalis were isolated from the 2 cefoxitin-treated patients who were considered bacteriologically unsatisfactory. All enterococci pathogens isolated were resistant to both study drugs while no sensitivity testing was performed on G. vaginalis.

In the remaining 13 patients (10 cefotetan and 3 on cefoxitin) polymicrobial pathogens were isolated from the patients who were considered bacteriologically unsatisfactory. In the polymicrobial aerobic group, a total of 10 different pathogens were isolated. Most pathogens isolated were Gram positive. Enterococci, resistant to both study drugs, were isolated more frequently than any of the polymicrobial aerobic pathogens.

In the polymicrobial aerobic and anaerobic group, a total of 16 different pathogens were isolated from the bacteriologically unsatisfactory patients. Nine Gram positive and seven Gram negative different pathogens were isolated. In the Gram positive group, Enterococcus was isolated most frequently. E. coli, B. fragilis, and B. capillosus were the most frequently isolated Gram negative pathogens.

Bacteriologic response could not be determined in 14 patients, primarily because, though the patient was a clinical failure, there was no growth on follow-up culture.

The mean cefotetan plasma level in the 132 patients test was 98 micrograms/ml at 88 minutes after dosing.

g. Conclusions

One dose of cefotetan, administered after clamping of the umbilical cord, was as safe and effective as three to five doses of cefoxitin, administered in prevention of post-operative infections following cesarean section surgery. Cefoxitin has an approved prophylaxis claim for use following cesarean section.

3. Hysterectomy - Abdominal and Vaginal

Protocol Title:

Multicenter, Open Comparative Study of Intravenous Cefotetan and Mefoxin (cefoxitin sodium) as Prophylactic Agents in Women Undergoing Vaginal or Abdominal Hysterectomy

a. Investigators

Denis Cavanagh, M.D.
William Ledger, M.D.
James Orr, M.D.
Jospeh G. Pastorek, II, M.D.
Bernd-Uwe Sevin, M.D.

b. Study Design

This was an open, multicenter, randomized study comparing intravenous cefotetan with intravenous cefoxitin in the prophylactic treatment of hospitalized women undergoing vaginal or abdominal hysterectomy. Uterocervical and urine cultures were obtained 24 hours prior to surgery, and cuff and urine cultures 24 hours after surgery plus cuff cultures 3 days following surgery. In abdominal hysterectomy cases, a culture of the surgical wound at closure was obtained. Pathogens isolated were identified and sensitivity tested. Finally, plasma and uterine tissues were obtained from the cefotetan-treated patients to assay for drug concentrations.

c. Criteria for Evaluability

These criteria were identical to the two previously reviewed protocols, with the following modification.

1. A uretrocervical culture was obtained 24 hours prior to prophylaxis.

Efficacy Evaluation

Clinical Response

The patient's clinical response to the prophylactic course of treatment was assessed as either a success, failure or unevaluable according to the following definitions.

Success

The clinical response was considered successful if no signs and symptoms of infection developed within the postoperative period up to the patient's scheduled follow-up evaluation visit.

Failure

The clinical response was considered a failure if the patient developed the clinical signs and symptoms of an infectious process which necessitated the need for antibiotics and/or surgical intervention. Febrile morbidity was defined as: oral temperature 100.4°F (38°C) or more on two consecutive readings at least six hours apart, excluding the first 48 postoperative hours.

The clinical response was also considered a failure if a patient showed evidence of any one or more of the following: urinary tract infection; wound infection; pelvic cellulitis; parametritis; endometritis; pelvic abscess or septic pelvic thrombophlebitis. Futhermore, if a chest x-ray was required because of a suspected pulmonary infection or an unidentified fever, the patient's clinical response was assessed as a failure.

Unable to Evaluate

No evaluation of the clinical response could be made.

Bacteriologic Response

Bacteriologic response was to be assessed based on the following cultures: 1) urine 24 hours prior to treatment; 2) uterocervical area 24 hours prior to treatment; 3) surgical wound (abdominal) at closure; 4) vaginal cuff on postoperative days one and three, and urine 24 hours postoperatively; and 5) additional cultures from any appropriate site when evidence of infection existed either during hospitalization or at the follow-up visit 7 to 10 days after discharge from the hospital.

According to these criteria, bacteriologic responses were defined as:

Satisfactory: The bacteriologic response was considered satisfactory provided that for all post-surgery cultures, prior to discharge, no evidence of bacteriologic pathogens was found and no infection developed.

Unsatisfactory: The bacteriologic response was considered unsatisfactory if any pre-discharge culture had any positive growth. The bacteriologic response was also considered unsatisfactory if two consecutive blood cultures were positive in a patient with sepsis.

Unable to Evaluate: The bacteriologic response was unable to be evaluated if the patient was prematurely lost to study because of voluntary withdrawal or relocation of residence.

d. Number of patients

One hundred and sixty-one patients were entered into this study, 132 were evaluable for efficacy analysis (87 cefotetan-treated patients and 45 cefoxitin-treated patients).

The patient evaluability by investigator is shown in the following Table 1.

e. Test Drug Schedule

The cefotetan-treated patients received 2 gm intravenously 30 to 60 minutes before surgery. Cefoxitin-treated patients received 2 gm administered intravenously 30 to 60 minutes before surgery and 2 gm, every 6 hours after the first dose for no more than 24 hours. Within each center, patients were randomized to cefotetan or cefoxitin in a 2 to 1 ratio.

f. Results

Efficacy

The clinical course of patients given prophylaxis was unsatisfactory in 13% of the vaginal and 22% of the abdominal hysterectomy patients given cefotetan, and in 25% of the vaginal and 18% if the abdominal hysterectomy patients given cefoxitin. Bacteriologically demonstrated infections were seen in 13% of the vaginal and 15% of the abdominal hysterectomy patients given cefotetan, and 29% of the vaginal and 18% of the abdominal hysterectomy patients given cefoxitin.

Safety

The safety and tolerance of intravenous cefotetan and cefoxitin were not different. No drug-related adverse signs and symptoms were reported in the cefotetan-treated and cefoxitin-treated patients.

The following tables and comments delineate in more detail the results of the study.

Table 1. Patient Evaluability by Investigator

Hysterectomy

Investigator	Total Number	Randomized Study Drug: Cefotetan Evaluable	Cefotetan Non-Evaluable	Cefotetan Total	Cefoxitin Evaluable	Cefoxitin Non-Evaluable	Cefoxitin Total
Dr. Cavanagh	31	14	6	20	7	4	11
Dr. Ledger	36	21	2	23	10	3	13
Dr. Orr	54	32	5	37	16	1	17
Dr. Pasterok	33	17	6	23	9	1	10
Dr. Sevin	7	3	1	4	3	0	3
TOTAL	161	87 (81%)	20 (19%)	107	45 (83%)	9 (17%)	54

Table 2. Type and Duration of Procedures

Hysterectomy

	Randomized Drug	
	Cefotetan N=87	Cefoxitin N=45
Surgical Procedure		
Vaginal Hysterectomy	47	28
Abdominal Hysterectomy	40	17
Frequency of Dosing/Grams per Dose		
One/2	87	0
Two/2	0	2
Three/2	0	33
Four/2	0	6
Five/2	0	4
Duration of Surgery (minutes)		
Mean	101.0	103.1
Median	95.0	90.0
Range	39-225	35-235
Duration of Post-Surgery Hospitalization Stay (days)		
Mean	6.7	6.2
Median	6.0	6.0
Range	4-22	4-10
Maximum Increase in Pre-Treatment* Temperature (°F)		
Number with Data Available	87	45
Mean	1.8	1.7
Median	1.8	1.5
Range	-0.2 to 4.8	0.2 to 5.4
Grading of Post-Treatment Surgical Wounds		
Number with Data Available	39	17
No erythema or discharge (Grade 0)	26 (67%)	14 (82%)
Cellulitis with or without minimal purulent exudate (Grade 1)	12 (30%)	3 (18%)
Cellulitis with moderate purulent exudate (Grade 2)	0 (0%)	0 (0%)
Infection throughout wound or intra-abdominal abscess (Grade 3)	1 (3%)	0 (0%)

* A negative number indicates change was a decrease in temperature.

Table 3. Investigator Response Summary/Overall Response Summary

Evaluable Vaginal Hysterectomy Patients

Investigator/Treatment	Number of Evaluable Patients	Clinical Response				Bacteriologic Response					
		Success		Failure		Satisfactory		Unsatisfactory		Cannot Determine	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cavanagh											
Cefotetan	11	9	(82)	2	(18)	9	(82)	2	(18)	0	(0)
Cefoxitin	6	4	(67)	2	(33)	4	(67)	2	(33)	0	(0)
Ledger											
Cefotetan	6	6	(100)	0	(0)	6	(100)	0	(0)	0	(0)
Cefoxitin	2	2	(100)	0	(0)	2	(100)	0	(0)	0	(0)
Orr											
Cefotetan	19	18	(95)	1	(5)	18	(95)	0	(0)	1	(5)
Cefoxitin	12	9	(75)	3	(25)	8	(67)	3	(25)	1	(8)
Pastorek											
Cefotetan	10	7	(70)	3	(30)	7	(70)	3	(30)	0	(0)
Cefoxitin	7	5	(71)	2	(29)	5	(72)	1	(14)	1	(14)
Sevin											
Cefotetan	1	1	(100)	0	(0)	1	(100)	0	(0)	0	(0)
Cefoxitin	1	1	(100)	0	(0)	1	(100)	0	(0)	0	(0)
TOTALS											
Cefotetan	47	41	(87)	6	(13)	41	(87)	5	(11)	1	(2)
Cefoxitin	28	21	(75)	7	(25)	20	(71)	6	(21)	2	(7)

Table 4. Investigator Response Summary/Overall Response Summary

Evaluable Abdominal Hysterectomy Patients

Investigator/Treatment	Number of Evaluable Patients	Clinical Response				Bacteriologic Response					
		Success		Failure		Satisfactory		Unsatisfactory		Cannot Determine	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cavanagh											
Cefotetan	3	2	(67)	1	(33)	2	(67)	0	(0)	1	(33)
Cefoxitin	1	0	(0)	1	(100)	0	(0)	1	(100)	0	(0)
Ledger											
Cefotetan	15	12	(80)	3	(20)	13	(87)	2	(13)	0	(0)
Cefoxitin	8	7	(88)	1	(12)	7	(88)	1	(12)	0	(0)
Orr											
Cefotetan	13	12	(92)	1	(8)	12	(92)	1	(8)	0	(0)
Cefoxitin	4	3	(75)	1	(25)	3	(75)	1	(25)	0	(0)
Pastorek											
Cefotetan	7	3	(43)	4	(57)	5	(71)	2	(29)	0	(0)
Cefoxitin	2	2	(100)	0	(0)	2	(100)	0	(0)	0	(0)
Sevin											
Cefotetan	2	2	(100)	0	(0)	2	(100)	0	(0)	0	(0)
Cefoxitin	2	2	(100)	0	(0)	2	(100)	0	(0)	0	(0)
TOTALS											
Cefotetan	40	31	(78)	9	(22)	34	(85)	5	(13)	1	(2)
Cefoxitin	17	14	(82)	3	(18)	14	(82)	2	(12)	0	(0)

Table 5. Reasons for Clinical Failure Among Evaluable Cases

Hysterectomy

Reason	Cefotetan	Cefoxitin
Cuff Induration	1	1
Cuff Cellulitis	1	1
Cuff Cellulitis/Febrile Morbidity	4	1
Urinary Tract Infection	2	3
Urinary Tract Infection/Febrile Morbidity	0	1
Febrile Morbidity	3	1
Pelvic Abscess	0	2
Pelvic Abscess/Febrile Morbidity	1	0
Pelvic Hematoma/Febrile Morbidity	1	0
Wound Infection/Febrile Morbidity	2	0
TOTALS	15	10

Bacteriologic Response

There were 7 patients (3 on cefotetan and 4 on cefoxitin) who had unsatisfactory bacteriologic responses with single pathogens isolated. In the cefotetan group, all of the enterococci isolated were resistant to cefotetan. The 3 cefotetan patients with unsatisfactory bacteriologic responses were also clinical failures because of a urinary tract infection, a vaginal cuff cellulitis and an infected wound hematoma. In the 4 cefoxitin-treated patients where single pathogens were isolated, sensitivities were not carried out on the enterococcus while Enterobacter cloacae was resistant. The E. coli strain isolated was susceptible to cefoxitin. All cefoxitin patients with unsatisfactory bacteriologic responses were also clinical failures. There were 2 reports of both cuff cellulitis and urinary tract infections.

A total of 23 polymicrobial aerobic pathogens were isolated from 8 patients, 4 on cefotetan and 4 on cefoxitin, who had bacteriologic unsatisfactory responses. The most frequent gram positive pathogens isolated were Enterococcus and Strep. alpha-hemolytic, while E. coli was the most frequent gram negative pathogen. Similarly, a total of 23 polymicrobial aerobic and anaerobic pathogens were isolated from 4 patients, 3 on cefotetan and 1 on cefoxitin, who had unsatisfactory responses. The most frequent gram positive pathogens isolated were Enterococcus and S. epidermidis coagulase negative. The most frequent gram negative pathogens were E. coli and B. fragilis.

9. CONCLUSION

One dose of cefotetan administered intravenously before surgery was as safe and effective as cefoxitin administered once before surgery and one to four times after surgery, in preventing postoperative infections in patients following vaginal or abdominal hysterectomy.

b. UNEVALUABLE STUDIES

The remainder of the prophylaxis studies submitted are unevaluable for the following reasons.

4. Colorectal Surgery

The United States studies submitted have too few evaluable patients on which to base a decision - 26 receiving cefotetan and 14 cefoxitin. It would be more appropriate to combine all of the gastrointestinal surgery studies since gastrointestinal surgery is the prophylaxis claim granted to other cephalosporins.

5. Biliary Tract Surgery

The United States studies submitted have too few evaluable patients on which to base a decision - 16 cefotetan and 4 cefoxitin. Although it is supported by a United Kingdom study involving 74 cefotetan patients and 79 cefazolin patients, the cefazolin regimen was single dose prophylaxis - a regimen not approved in the United States.

6. Appendical Surgery

The United States studies submitted have too few evaluable patients on which to base a decision - 4 receiving cefotetan and 3 cefoxitin.

7. Upper GI Surgery

Only one United States study was submitted and only 4 cefotetan patients and 1 cefoxitin patient were evaluable.

8. United Kingdom Studies

These studies were unevaluable because they were conducted using either drugs or regimens which do not have approved prophylaxis claims in the United States.

These comparative agents were:

a. metronidazole (used in the colorectal and appendical surgery prophylaxis studies).

b. gentamicin (used in the transurethral and acute abdominal [here concomitantly with tinidazole] surgery prophylaxis

c. cefazolin single dose prophylaxis in biliary tract surgery - a regimen not approved in the United States.

C. Overall Conclusions Concerning Prophylaxis

The applicant has demonstrated in controlled comparative trials using antibiotics with appropriate, approved, prophylaxis claims that cefotetan is as safe and effective as the comparative agent studied for the following indications.

a. hysterectomy (abdominal and vaginal)

b. cesarean section

c. transurethral prostatectomy

G. Overall Conclusions - Comparative Studies

1. Efficacy

The combined results of the comparative studies submitted are summarized in the following tables. These tables represent the patients found evaluable by this reviewer.

a. Urinary Tact Infections

Table a. Bacteriological Response by Pathogen for Controlled Urinary Infection Studies

Pathogens	Cefotetan-Treated Patients Satisfactory Response/Total	%	Cefoxitin-Treated Patients Satisfactory Response/Total	%
E. coli	252/270	93	100/118	85
K. pneumoniae	60/62	97	20/22	91
K. oxytoca	0		1/1	
Klebsiella sp.	11/14	79	2/2	
Enterobacter sp.	7/7	100	0	
P. mirabilis	56/60	93	16/19	84
Proteus, indole-pos.	11/11	100	2/4	50
M. morganii	0		2/2	
Pr. rettgeri	0		1/1	
Citrobacter sp.	3/5	60	0	
Ser. marcescens	0/1		0	
Ps. aeruginosa	1/1		0	
Ps. cepacia	0		1/1	
Acinetobacter sp.	0		1/1	
S. epidermidis	3/3		0	
Str. agalactiae	0		1/1	
Streptococcus sp.	1/3	33	0	
Diptheroids	1/1		0	
Lactobacillus sp.	0/1			

It is concluded from these studies that cefotetan is as effective as cefoxitin in the treatment of urinary tract infections caused by:

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis.

b. Lower Respiratory Tract Infections

Table b. Bacteriological Response by Pathogen for Controlled Lower Respiratory Infection Studies

Pathogens	Cefotetan-Treated Patients Satisfactory Response/Total	%	Moxalactam-Treated Patients Satisfactory Response/Total	%
S. aureus	13/13	100	7/7	
Str. pneumoniae	28/35	80	11/11	
Streptococcus sp.	3/3	100	3/3	
E. coli	14/14	100	8/8	
K. pneumoniae	12/12	100	7/7	
Klebsiella sp.	4/5	80	1/1	
Enterobacter sp.	8/11	73	2/3	67
Proteus mirabilis	4/4	100	1/3	33
Serratia sp.	4/5	80	0	
H. influenzae	21/27	78	14/14	
Haemophilus sp.	3/3		0	
Citrobacter sp.	4/5	80	0	
Pseudomonas sp.	2/2		2/2	
Other gram-neg.	2/2		2/2	

It is concluded from these studies that cefotetan is as effective as moxalactam in the treatment of respiratory tract infections caused by:

Streptococcus pneumoniae
Haemophilus influenzae.

c. Skin and Skin Structure Infections

Table c. Bacteriological Response by Pathogen for Controlled Skin/Skin Structure Infection Studies

Pathogens	Cefotetan-Treated Patients Satisfactory Response/Total	%	Cefotaxime-Treated Patients Satisfactory Response/Total	%
S. aureus	16/17	94	4/5	80
S. epidermidis	2/3	67	2/2	
Staphylococcus sp.	0		1/1	
Str. pyogenes	2/2	100	0	
Str. agalactiae	3/3	100	0	
Streptococcus sp.	1/1	100	5/5	100
Diptheroids	0		1/1	
E. coli	2/4	50	0/1	
K. oxytoca	0		1/1	
E. cloacae	0		0/1	
Enterobacter sp.	2/2	100	0	
P. mirabilis	5/6	83	2/2	
Proteus, indole pos.	0		1/2	
Ser. marcescens	0/1		0	
Salmonella sp.	1/1	100	0	
Ps. aeruginosa	0		1/1	
Pseudomonas sp.	1/1	100	0	
Aero. hydrophilia	0		1/1	
B. fragilis	0/1		0	
Bacteroides sp.	1/1	100	0	

Too few patients were studied to be able to conclude that cefotetan is as effective as cefotaxime for any causitive organism of skin and skin structure infections.

d. Gynecologic Infections

Table d. Bacteriological Response by Pathogen for Controlled Gynecologic Infection Studies

Pathogens	Cefotetan-Treated Patients Satisfactory Response/Total	%	Moxalactam-Treated Patients Satisfactory Response/Total	%
Str. agalactiae	1/1	100	0	
Streptococcus sp.	1/1	100	0	
E. coli	0		2/2	100
K. oxytoca	0		1/1	100
Enterobacter sp.	1/1	100	0	
Acinetobacter sp.	1/1	100	0	
N. gonorrhea	8/8	100	4/4	100
B. bivius	1/1	100	0	
B. melaninogenicus	1/1	100	0	
Bacteroides sp.	0		1/1	100
Fusobacterium sp.	1/1	100	0	
Other anaerobes	1/1	100	0	

Too few patients were studied to be able to conclude that cefotetan is as effective as moxalactam for any causitive organism of gynecologic infections

e. Intra-abdominal Infections

Table e. Bacteriological Response by Pathogen for Controlled Intra-Abdominal Infection Studies

Pathogens	Cefotetan-Treated Patients Satisfactory Response/Total	%	Moxalactam-Treated Patient Satisfactory Response/Total	%
S. aureus	1/1	100	0	
Streptococcus sp.	3/3	100	2/2	100
Enterococcus	1/1	100	0	
E. coli	2/2	100	1/1	100
P. mirabilis	0		0/1	
B. fragilis	2/2	100	0	
Clostridium sp.	3/3	100	0	
Eik. corrodens	0		1/1	100
Ps. aeruginosa	0		1/1	100
Fusobacterium sp.	0		1/1	100

Too few patients were studied to be able to conclude that cefotetan is as effective as moxalactam for any causitive organism of intra-abdominal infections.

2. Safety

See the combined safety discussion at the conclusion of this review.

IV. UNCONTROLLED STUDIES

A. Lower Respiratory Tract Infections

1. Protocol 2-1-0-01. A multicenter, open non-comparative study of intravenous cefotetan in the treatment of hospitalized patients with lower respiratory tract infections.

Investigators

Richard S. Kronenberg, M.D.	Minneapolis, MN
Thomas Nolen, M.D.	Alabaster, AL
Rodney M. Snow, M.D.	Birmingham, AL

Study Design

The study, other than being non-comparative, was basically identical to the comparative studies previously reviewed. The same entry, exclusion, and efficacy criteria were used.

Cefotetan was administered by the intravenous route only. All patients except one were treated with 2 gm every 12 hours. One patient was treated with 3 gm every 12 hours. Most patients were treated for 5 to 10 days.

Results

Eighty-nine patients were entered into this study. Of these, 58 were evaluable for judging the efficacy of cefotetan and all 89 were included in the evaluation of safety.

Efficacy

Forty-nine of 58 evaluable patients had pneumonia. The remainder had bronchopneumonia (6), bronchitis (3), or empyema (1).

Complete clearing or substantial improvement in the clinical signs or symptoms of infection occurred in 53 patients (91%).

The bacteriologic response in this study is detailed in table 1 and 2.

Table 1. Bacteriologic Response

	Number of Evaluable Patients	Satisfactory with end Culture	Satisfactory no end Culture	Unsatisfactory
Pathogens				
Gram Negative				
Haemophilius sp.	1	1	0	0
H. influenzae	10	8	2	0
Klebsiella oxytoca	6	5	1	0
Klebsiella pneumoniae	6	1	4	1
Escherichia coli	6	4	2	0
Enterobacter aerogenes	3	3	0	0
Enterobacter cloacae	1	1	0	0
Proteus mirabilis	1	1	0	0
Serratia liquefaciens	1	1	0	0
Serratia marcescans	2	2	0	0
Gram Positive				
Streptococcus pneumoniae	10	3	6	1
Streptococcus not A or B	1	0	1	0
Staph aureus	4	2	2	0
Polymicrobial	6	2	3	1

Table 2 Incidence of Organisms in Polymicrobial Infections
Evaluable Patients

Pathogen in Polymicrobial Infections	Number of Occurrences	Bacteriologic Response		
		Satisfactory with end Culture	Satisfactory no end Culture	Unsatisfactory
Gram negative				
Haemophilus influenzae	3	1	2	0
Klebsiella oxytoca	2	1	1	0
Citrobacter diversus	1	0	0	1
Enterobacter cloacae	1	0	1	0
Proteus mirabilis	1	0	1	0
Serratia rubidaea	1	1	0	0
Gram positive				
Streptococcus pneumoniae	2	1	0	1
Streptococcus pyogenes	1	0	1	0

Table 3 Clinical and Radiographic Response
Evaluable Patients

Response	Clinical	Radiographic
Completely Cleared	35	12
Improved	18	31
No change	5	12
Worse	0	3

Safety

One case each of drug related diarrhea, redness at the injection site, and increased SGPT occurred in this study.

Therapy was not discontinued in any patient because of an adverse clinical effect or laboratory abnormality.

Conclusions

The cure rates in this open study of lower respiratory tract infections (95% overall) are comparable to those seen in the comparative studies with cefotetan (89%) and support the conclusion that cefotetan is safe and effective in the treatment of lower respiratory tract infections such as pneumonia and bronchopneumonia.

B. Infections cause by Susceptible Bacteria

1. Proctocol 2-9-0-01. A multicenter, open, noncomparative study of parenteral cefotetan in the treatment of hospitalized patients with infections caused by susceptible bacteria.

a. Investigators

John A. Boswick, M.D.	Denver, CO
Michael A. Castellano, M.D.	Staten Island, NY
Isidore Chon, Jr., M.D.	New Orleans, LA
Roger M. Echols, M.D.	Albany, NY
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Richard L. Sweet, M.D.	San Francisco, CA

b. Study Design

The study was similar in design to the studies previously reviewed, except rather than being limited to one kind of infection, patients with the following bacterial infections could be studied.

1. Urinary tract infections

2. Lower respiratory tract infections

3. Skin and skin structure infections including surgical wound infections

4. Intraabdominal (surgical) infections

5. Gynecological infections

6. Bacteremia/septicemia

7. Bone and Joint infections

8. Other infections that could be appropriately treated with parenteral cefotetan

Treatment with cefotetan was by the intravenous route. The dosage depended on the severity of the infection and the susceptibility of the causative organism and ranged from 500 mg to 3 grams every 12 hours. Duration of therapy was for a minimum of five days with continuation at the discretion of the investigator. No other antimicrobial therapy was to be given durig the treatment period and, for urinary tract infections, during the 5-9 days follow up.

Inclusion, exclusion, evaluability, and efficacy criteria were essentially identical to those in the protocols reviewed earlier.

c. Evaluable Patients

The sponsor found 298 patients evaluable. This reviewer found the following additional 22 patients unevaluable.

Study	Page No.	Patient No.	Drug	Reason for Non-Evaluability
Open 2-9-0-01 SSS				
	26	50	CTN	Less than five days treatment
	33	8	CTN	Less than five days treatment
	36	37	CTN	Less than five days treatment
	42	19	CTN	Less than five days treatment/ Sensitivities not obtained
	49	52	CTN	Less than five days treatment
	53	62	CTN	Foot amputated
Gyn				
	60	37	CTN	Less than five days treatment
	64	16	CTN	Less than five days treatment
	65	14	CTN	Less than five days treatment
	67	8	CTN	Less than five days treatment
	67	12	CTN	Less than five days treatment
	72	1	CTN	Sensitivities not obtained
	72	5	CTN	Less than five days treatment
	72	10	CTN	Less than five days treatment
	73	13	CTN	Less than five days treatment
	73	17	CTN	Sensitivities not obtained
UTI				
	75	56	CTN	No post-Rx culture obtained
	75	73	CTN	No post-Rx culture obtained
	78	18	CTN	Other antimicrobial drug Rx
	81	5	CTN	No post-Rx culture obtained
B&J				
	90	67	CTN	Surgical intervention
	94	2	CTN	Inadequate treatment period for osteo

Additionally, the following changes were made by this reviewer in cases found evaluable by the sponsor.

EVALUABLE CASES REQUIRING CHANGES

STUDY	PAGE NO.	PATIENT NO.	DRUG	CHANGES MADE
Open 2-9-0-01 SSS				
	43	1	CTN	S. aureus deleted
	43	3	CTN	Peptostreptococcus sp., Bacteroides sp., Propionibacterium sp., and Veillonella sp. deleted
	48	46	CTN	STR, Alpha-hem deleted
	48	47	CTN	P. mirabilis, E. coli, C. freundii, STR, Alpha-hem deleted
	49	50	CTN	STR, non-hem deleted
	54	3	CTN	B. fragilis, Peptococcus sp., Bacteroides sp. deleted
GYN				
	68	6	CTN	N. gonorrhoeae deleted
	68	12	CTN	STR, Alpha-hem and S. aureus deleted
	69	33	CTN	F. necrophorum does have MIC value: not deleted
	70	44	CTN	Str. pyogenes deleted (throat culture)
	74	18	CTN	B. asaccharolyticus, STR (non-en) Grp D, and Bacteroides #1 deleted
	74	19	CTN	STR, Grp D deleted
UTI				
	78	25	CTN	P. mirabilis deleted
LRI				
	88	9	CTN	STR, not Grp A, B, or D deleted
I/A				
	97	20	CTN	Ent cloacae deleted

Of the 276 patients finally found evaluable, 141 had skin and skin structure infections, 84 had gynecological infections, 17 had urinary tract infections, 15 had lower respiratory tract infections, 9 had bone and joint infections, 8 had intra-abdominal infections, and 2 had septicemia. Patients were evenly distributed by age decade from age 20 to age 80.

Diagnoses by the type of infection are listed in Table 1.

Table 1 Primary Diagnoses
Evaluable Patients

Clincal Diagnosis	Number of Patients
Skin and Skin Structure	
Abscess	11
Abscess with Cellulitis, Post-Traumatic	1
Abscess with Cellulitis	2
Acne Conglobata	1
Cellulitis	55
Cellulitis with Paronychia	1
Cellulitis/Bacteremia	3
Cellulitis, Post-Operative	1
Cellulitis, Post-Traumatic	10
Infected Burn	1
Infection, Post-Traumatic	3
Injection Site Infection/Bacteremia	1
Paronychia	2
Parotitis	1
Skin Graft Infection	1
Soft Tissue Infection, Basal Cell CA	1
Soft Tissue Infection	2
Ulcer with Cellulitis	4
Wound Infection, Post-Operative/Bacteremia	1
Wound Infection	3
Wound Infection, Post-Operative	20
Wound Infection, Post-Traumatic	16
Total	141
Gynecological	
Gonorrhea	1
Pelvic Inflammatory Disease	32
Endometritis	2
Endometritis, Post Partum	31
Endometritis, Post Partum/Bacteremia	1
Endomyometritis	1
Vaginal Cuff Cellulitis	1

Table 1 Primary Diagnoses (Cont'd.)
Evaluable Patients

Clinical Diagnosis		Number of Patients
Gynecological (Cont'd)		
Chorioamnionitis		1
Endomyometritis, Post Partum		1
Endomyoparametritis, Post Partum		5
Endoparametritis, Post Partum		6
	Total	82
Urinary Tract		
Cystitis		2
Pyelonephritis		5
UTI, not otherwise specified		6
UTI/Bacteremia		4
	Total	17
Lower Respiratory Tract		
Pneumonia		12
Pneumonia/Bacteremia		3
	Total	15
Bone and Joint		
Osteomyelitis		4
Infected Prosthesis		1
Septic Artritis		1
Septic Bursitis		3
	Total	9
Intraabdominal		
Ruptured Appendix		2
Gangrenous Appendix		2
Toxic Megacolon		1
Intra-Abdominal Abscess		1
Biliary Tract Infection		1
Intra-Abdominal Sepsis		1
	Total	8
Septicemia		
Septicemia		2
	Total	2

d. Efficacy

1. Skin and Skin Structure Infections - Open Studies

Two hundred and thirty seven patiens were entered by 15 investigators-141 were evaluable. The most common reasons for nonevaluability were no pathogen isolated or a resistant pathogen isolated. Dosage ranged from 1.0 to 3.0 gm q12h with 58% of the patients receiving 2 gm q12h. The mean duration of treatment was 8.9 days.

Bacteriological and clinical response is given in Tables 2 and 3.

Table 2 Efficacy Summary, by Pathogen
Skin and Skin Structure Infections

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
E. Coli	6	5	1	6	0	0
Ent. cloacae	2	1	1	1	0	1
Kleb. pneumoniae	1	1	0	0	1	0
N. Gonorrhoeae	1	1	0	1	0	0
P. mirabilis	3	2	1	3	0	0
Pas. multocida	1	1	0	1	0	0
S. aureus, coag pos	45	44	1	38	7	0
S. aureus, pen R	1	1	0	1	0	0
S. epidermidis, coag neg	9	8	1	7	2	0
Ser. marcescens	2	2	0	2	0	0
Str. agalactiae, grp B	1	1	0	1	0	0
Str. intermedius	1	1	0	1	0	0
Str. pyogenes, grp A	17	17	0	17	0	0
Str. not Grop A or B	1	1	0	0	1	0
Str. alpha-hem	3	2	1	2	1	0
Peptococcus	1	1	0	1	0	0
Polymicrobial	46	41	5	34	9	3
Total	141	130 92%	11 8%	116 82%	21 15%	4 3%

Incidence of
Table 3 Organisms in Polymicrobial Infections
Evaluable Patients
Skin/Skin Structure Infections

	Organisms Eradicated
Aerobic Organisms	
Citrobacter diversus	1
Citrobacter sp.	1
Diptheroids	1
Enterobacter agglomerans	1
Enterobacter cloacae	2
Enterobacter sp.	1
Enterococcus	2/3
Enterococcus, beta-hem	0/1
Enterococcus, hem	2
Enterococcus, non-hem	2
Escherichia coli	4
Klebsiella oxytoca	1
Klebsiella pneumoniae	2
Klebsiella sp.	1
Morganella morganii	1
Proteus mirabilis	6/8
Proteus vulgaris	1
Providencia rettgeri	3
Staphylococcus albus	1
Staphylococcus aureus	31/33
Staphylococcus epidermidis	6
Streptococcus agalactiae	3
Streptococccus, alpha-hem	2
Streptococcus, Group C	1
Streptococcus, Group D	1
Streptococcus, Group G	2
Streptococcus, non-hem	0/1
Streptococcus, not Group A	1
Streptococcus, not Group A, B or D	2
Streptococcus pyogenes	19

Table 3 (Cont'd)

Incidence of
Organisms in Polymicrobial Infections
Evaluable Patients
Skin/Skin Structure Infections

	Organisms Eradicated
Anaerobic Organisms	
Anaerobic Micrococcus	1
Anaerobic Streptococcus	0/2
Bacteroides fragilis	3
Bacteroides melaninogenicus	1
Bifidobacterium sp.	1
Fusobacterium nucleatum	1
Microaerophilic Micrococcus	1
Microaerophilic Streptococcus	1
Peptococcus assacharolyticus	1
Peptostreptococcus sp.	2

2. Gynecological Infections - Open Studies

Of 175 patients with gyneclogic infections entered by 10 investigators, 82 were evaluable. The most common reason for nonevaluability was no organism isolated pretreatment.

Dosage regimens ranged from 1 to 3 gm q12h, with 65% of patients receiving 2 gm q12h. The mean duration of therapy was 5.6 days.

Bacteriological and clinical response is given in Tables 4 and 5.

Table 4 Efficacy Summary, by Pathogen
Gynecological Infections

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
Ac. fermentans	1	1	0	1	0	0
Bacteroides melaninogenicus	1	1	0	1	0	0
Citro freundii	1	1	0	1	0	0
E. coli	2	2	0	2	0	0
Fusobacterium sp.	1	1	0	1	0	0
H. parainfluenzae	1	1	0	1	0	0
H. vaginalis	1	1	0	1	0	0
Kleb. pneumoniae	2	2	0	2	0	0
N. gonorrhoeae	7	7	0	7	0	0
N. gonorrhoeae, pen s	1	1	0	1	0	0
P. mirabilis	1	1	0	1	0	0
Streptococcus sp.	1	1	0	1	0	0
S. epidermidis, coag neg	1	1	0	1	0	0
Str. agalactiae, grp B	3	3	0	3	0	0
Str. alpha hem	1	1	0	1	0	0
Str. pyogenes, grp A	3	3	0	3	0	0
Str., grp D	1	1	0	1	0	0
Polymicrobial	53	49	4	51	1	1
Total	82	78 95%	4 5%	79 98%	1	1 1%

Table 5 Incidence of Organisms, Polymicrobial Infections
Evaluable Patients
Gynecological Infections

	Organisms Eradicated
Aerobic Organisms	
Corynebacterium sp	1
Enterobacter cloacae	3
Enterobacter aerogenes	1
Escherichia coli	15/16
Haemophilus vaginalis	4/6
Haemophilus parainfluenzae	1
Klebsiella pneumoniae	3
Neisseria gonorrhoea	16
Proteus mirabilis	8
Staphylococcus aureus (includes methicillin resistant	5
Staphylococcus epidermidis	13
Streptococcus agalactiae (Group B)	13/14
Streptococcus, Group A	2
Streptococcus, Group D (no further identification)	10
Streptococcus, Group D - Enterococcus	7
Streptococcus, Group D - nonenterococcus	3
Streptococcus, alpha hemolytic	3
Streptococcus, nonhemolytic	2
Streptococcus intermedius	1
Streptococcus sp.	1
Streptococcus virdidans	2
Anaerobic Organisms	
Bacteroides fragilis	3
Bacteroides thetaiotaomicron	1
Bacteroides bivius	7
Bacteroides asaccharolyticus	2
Bacteroides disiens	2
Bacteroides melaninogenicus	3
Bacteroides sp.	9/11
Clostridium sp.	1
Fusobacterium sp.	4
Fusobacterium mortiferum - varium group	1
Gaffkya anaerobia	1
Gram negative cocci, unspeciated	1

Table 5 (Cont'd)
Incidence of Organisms, Polymicrobial Infections
Evaluable Patients
Gynecological Infections

	Organisms Eradicated
Gram positive cocci, unspeciated	1
Peptococcus asaccharolyticus	2
Peptococcus magnus	1
Petostreptococcus anaerobius	3
Veillonella parvula	3

3. Urinary Tract Infections - Open Studies

Of 44 patients with urinary tract infections entered by 10 investigators, 17 were evaluable. Most of the nonevaluable patients had either a resistant organism, no organism isolated pretherapy, or no follow-up cultures.

Most patients (67%) had complicated urinary tract infections, 24% had polymicrobial infections, and 43% had an indwelling urinary catheter.

Table 6 Efficacy, by Pathogen
Urinary Tract Infections

	Number of Patients	Bacteriologic Response				Clinical Response		
		Cure with Super Cure	Cure with Super Infection	Failure with Super Failure	Failure with Super Infection	Cleared	Improved	No Change
Single Pathogens								
E. coli	8	4	3	1	0	7	0	1
Ent. aerogenes	2	2	0	0	0	2	0	0
Kleb. pneumoniae	3	1	2	0	0	3	0	0
S. aureus, coag pos	1	1	0	0	0	1	0	0
Polymicrobial	3	2	0	1	0	2	0	1
Total	17	10 59%	5 29%	2 12%	0 0%	15 88%	0	2 12%

4. Lower Respiratory Tract Infections - Open Studies

Of 39 patients with lower respiratory tract infections entered by 8 investigators, 15 were evaluable. The most common reason for exclusion was no organism isolated.

Table 7 Efficacy, by Pathogen
Lower Respiratory Tract

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
Bran. catarrhalis	1	1	0	1	0	0
E. coli	1	1	0	1	0	0
H. influenzae	5	5	0	4	1	0
Kleb. pneumoniae	1	0	1	0	0	1
S. aureus, coag pos	1	1	0	1	0	0
Str. pneumoniae	3	3	0	2	1	0
Polymicrobial	3	3	0	3	0	0
Total	15	14 93%	1 7%	12 80%	2 13%	1 7%

5. Bone and Joint Infections - Open Studies

Fifteen patients with bone and joint infections were entered by 8 investigators. Nine were evaluable. The usual dose was 2 gm of q12h for a mean duration of 14.9 days.

Table 8 Efficacy Summary, by Pathogen
Bone and Joint

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change or Worse
Single Pathogens						
S. aureus, coag pos	6	6	0	6	0	0
Str. pyogenes, grp A	1	1	0	1	0	0
Polymicrobial	2	2	0	2	0	0
Total	9	9 100%	0 0%			0 0%

The two polymicrobial infections which were cured were an infection with Staphylococcus aureus and Streptococcus pyogenes, and an infection with Klebsiella pneumoniae and Streptococcus aglactiae.

6. Intrabdominal Infections - Open Studies

Eight of 31 patients studied by four investigators were evaluable for efficacy.

Table 9 Efficacy Summary, by Pathogen
Bone and Joint

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
E. coli	2	1	1	0	1	1
S. albus	1	1	0	1	0	0
Klebsiella pneumoniae	1	1	0	1	0	0
Polymicrobial	5	4	0	1	3	0
Total	8	7 88%	1 12%	3 38%	4 50%	1 12%

Table 8 Efficacy Summary, by Pathogen
Bone and Joint

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change or Worse
Single Pathogens						
S. aureus, coag pos	6	6	0	6	0	0
Str. pyogenes, grp A	1	1	0	1	0	0
Polymicrobial	2	2	0	2	0	0
Total	9	9 100%	0 0%			0 0%

The two polymicrobial infections which were cured were an infection with Staphylococcus aureus and Streptococcus pyogenes, and an infection with Klebsiella pneumoniae and Streptococcus aglactiae.

6. Intrabdominal Infections - Open Studies

Eight of 31 patients studied by four investigators were evaluable for efficacy.

Table 9 Efficacy Summary, by Pathogen
Bone and Joint

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
E. coli	2	1	1	0	1	1
S. albus	1	1	0	1	0	0
Klebsiella pneumoniae	1	1	0	1	0	0
Polymicrobial	5	4	0	1	3	0
Total	8	7 88%	1 12%	3 38%	4 50%	1 12%

Table 10 Incidence of Organisms, Polymicrobial Infections
Evaluable Patients
Intraabdominal Infections

	Number of Patients Cured
Aerobic Organisms	
Escherichia coli	5
Klebsiella oxytoca	1
Morganella morganii	1
Proteus mirabilis	2
Streptococcus Group D - Enterococcus	1
Anaerobic Organisms	
Bacteroides fragilis	1

7. Septicemia - Open Studies

Two of Four patients studied by the investigators were evaluable.

Table 11 Summary, by Pathogen
Septicemia

	Number of Patients	Bacteriologic Response		Clinical Response		
		Satis-factory	Unsatis-factory	Cleared	Improved	No Change
Single Pathogens						
S. aureus, coag pos	1	1	0	1	0	0
Str. pneumoniae	1	1	0	1	0	0
Total	2	2 100%	0 0%	2 100%	0 0%	0 0%

C. Summary of Efficacy in Uncontrolled Studies

The following tables 1 through 6 summarize the efficacy results of cefotetan in the uncontrolled trials which were submitted.

Uncontrolled Studies

Table 1 Bacteriological Response by Pathogen for Urinary Infections Treated with Cefotetan

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
E. coli	11	3	14	13 (93%)	1 (7%)
Kleb. pneumoniae	3	0	3	3	0
Enterobacter aerogenes	2	0	2	2	0
P. mirabilis	0	2	2	2	0
S. aureus	1	1	2	2	0

*Eradication of initial pathogen

Uncontrolled Studies

Table 2 Bacteriological Response by Pathogen for Lower Respiratory Infections Treated with Cefotetan

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
S. aureus	5	1	6	6	0
Str. pneumoniae	13	3	16	13 (81%)	3 (19%)
Streptococcus sp.	2	1	3	3	0
E. coli	7	0	7	7	0
K. pneumoniae	7	0	7	5 (71%)	2 (29%)
Klebsiella sp.	6	2	8	8	0
Enterobacter sp.	4	1	5	5	0
Proteus mirabilis	1	1	2	2	0
Serratia sp.	3	1	4	4	0
H. influenzae	15	5	20	20	0
Haemophilus sp.	1	0	1	1	0
Citrobacter sp.	0	1	1	0	1
Other gram-neg. sp.	1	0	1	1	0

*Includes patients in whom there was no material to culture because of clinical improvement

Uncontrolled Studies

Table 3 Bacteriological Response by Pathogen for All Intra-Abdominal Infections Treated with Cefotetan

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
S. epidermidis	1	0	1	1	0
Enterococcus	0	1	1	1	0
E. coli	1	5	6	5	1
Klebsiella sp.	0	2	2	2	0
Enterobacter sp.	0	1	1	1	0
P. mirabilis	0	2	2	2	0
Proteus, indole-positive	0	1	1	1	0
B. fragilis	0	1	1	1	0

*Includes patients in whom there was no material to culture because of clinical improvement

Uncontrolled Studies

Table 4 Bacteriological Response by Pathogen for Skin/Skin Structure Infections Treated with Cefotetan

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
S. aureus	45	36	81	77 (95%)	4 (5%)
S. epidermidis	8	8	16	14 (88%)	2 (12%)
Str. pyogenes	17	19	36	36	0
Str. agalactiae	1	4	5	4	1
Streptococcus sp.	5	16	21	20 (95%)	1 (5%)
Enterococcus	0	6	6	3	3
Diptheroids	0	1	1	1	0
E. coli	6	7	13	12 (92%)	1 (8%)
K. pneumoniae	1	2	3	3	0
Klebsiella sp.	0	2	2	2	0
Enterobacter sp.	2	4	6	5	1
P. mirabilis	2	9	11	8 (73%)	3 (27%)
Proteus, indole pos.	0	3	3	3	0
Citrobacter sp.	0	3	3	2	1
Ser. marcescens	2	0	2	2	0
Pasteurella sp.	1	0	1	1	0
N. gonorrhea	1	0	1	1	0
Providencia sp.	0	4	4	4	0
B. fragilis	0	5	5	4	1
B. melaninogenicus	0	3	3	3	0
Bacteroides sp.	0	3	3	2	1
Fusobacterium sp.	0	1	1	1	0
Propionibacterium sp.	0	1	1	1	0
Peptococcus sp.	0	4	4	3	1
Peptostreptococcus sp.	0	3	3	3	0
Veillonella sp.	0	1	1	1	0
Other anaerobes	0	7	7	2	5

*Includes patients in whom there was no material to culture because of clinical improvement

Uncontrolled Studies

Table 5 Bacteriological Response by Pathogen for Gynecologic Infections Treated with Cefotetan

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
S. aureus	0	6	6	6	0
S. epidermidis	2	14	16	16	0
Str. pyogenes	3	2	5	5	0
Str. agalactiae	3	13	16	15 (94%)	1 (6%)
Streptococcus sp.	4	25	29	27 (93%)	2 (7%)
Enterococcus	0	7	7	7	0
Corynebacterium sp.	0	1	1	1	0
E. coli	2	18	20	19 (95%)	1 (5%)
K. pneumoniae	2	3	5	4	1
Enterobacter sp.	0	4	4	4	0
P. mirabilis	3	9	12	12	0
Citrobacter sp.	2	0	2	2	0
Haemophilus sp.	2	8	10	9	1
N. gonorrhea	9	12	21	20 (95%)	1 (5%)
B. fragilis	0	2	2	2	0
B. melaninogenicus	0	4	4	4	0
B. bivius	1	7	8	7	1
Bacteroides sp.	0	13	13	10 (77%)	3 (23%)
Fusobacterium sp.	2	4	6	6	0
Clostridium sp.	0	2	2	2	0
Eubacterium sp.	0	1	1	1	0
Peptococcus sp.	1	7	8	8	0
Peptostreptococcus sp.	0	3	3	3	0
Veillonella sp.	0	3	3	2	1
Other anaerobes	2	6	8	8	0

*Includes patients in whom there was no material to culture because of clinical improvement

Table 6. Bacteriological Response by Pathogen for All Bone & Joint Infections Treated with Cefoteten

Pathogens	Number of Isolates			Bacteriological Response	
	Single Organism Infection	Polymicrobial Infection	Total	Satisfactory*	Unsatisfactory
S. aureus	6	2	8	8	0
Str. pyogenes	1	1	2	2	0
Str. agalactiae	0	1	1	1	0
Streptococcus sp.	0	1	1	1	0
K. pneumoniae	1	1	2	2	0

*Includes patients in whom there was no material to culture because of clinical improvement

V. Overall Summary

(1) Safety

a. Adverse Events

1. Efficacy Studies

A total of 1810 patients were treated in the North American clinical trials (table 1). Of these, 1451 patients received cefotetan, 233 received cefoxitin, 107 received moxalactam, and 19 received cefotaxime. Drug-realted adverse signs and symptoms i.e., those rated by the investigator as definitely or probably related to cefotetan were reported in 66 cefotetan-treated patients or 4.6% of the treated population. Drug-related events were reported in 5 of 233 patients treated with cefoxitin (2.1%), in 9 of 107 patients treated with moxalactam (8.4%), and one of 19 cefotaxime treated patients (5.2%).

The mean age for the cefotetan treated patients was 54, while the men age for cefotetan treated patients who had drug-related adverse signs and symptoms was 55. Overall, more males than females received cefotetan, while more females than males had drug-related adverse signs and symptoms.

Table 2 presents the age distribution for patients treated with each of the four drugs, and the number of patients within each group for whom drug-related side effects were reported. The number of patients in each age group having drug-related adverse effects was proportional to the total number of patients in the group, indicating that no particular age group was at risk for developing side effects.

The distribution of number of patients treated and number of drug-related side effects versus dosage administered is summarized in Table 3 for cefotetan and the comparative agents studied. For cefotetan-treated patients, the number of patients experiencing drug-related side effects was proportional to the total number of patients treated at each dose.

SIDE EFFECTS BY BODY SYSTEM
CEFOTETAN

Table 4A summarizes by body system the drug-related adverse signs and symptoms reported for patients treated with cefotetan. This table includes the side effects appraised by the investigator as being definitely or probably related to cefotetan.

LOCAL EFFECTS

There were 12 reports of local side effects which included five cases of injection site phlebitis (0.34%), and three of injection site discomfort (0.21%). There was one report each of injection site redness (0.07%), swelling (0.07%), forearm cellulitis (0.07%), and forearm swelling (.007%).

HYPERSENSITIVITY

Eighteen cases of drug-related hypersensitivity reactions were reported in the cefotetan-treated patients. The most frequently occurring reactions were rash (nine cases, 0.62%), and itching (two cases, 0.14%).

CARDIORESPIRATORY

One case of dyspnea was reported (0.07%)

GASTROINTESTINAL

Diarrhea was reported in 18 patients (1.24%). There were two reports of nausea (0.14%) and one of vomiting (0.07%).

GENITOURINARY

One case of monilial vaginitis was reported (0.07%).

MISCELLANEOUS

Reports of miscellaneous clinical drug-related adverse signs and symptoms were infrequent. The reports of miscellaneous adverse signs and symptoms consisted of two cases of mouth blisters (0.14%) and one case each of submandibular adenopathy (0.07%), sore mouth (0.07%) and sore throat (0.07%).

HEMOPOIETIC

Twenty hemopoietic laboratory test alterations reported for the cefotetan-treated patients were considered drug-related. The most frequently reported were eosinophilia (seven reports, 0.48%), positive direct Coombs test (six reports, 0.41%), and thrombocytosis (five reports, 0.34%).

HEPATIC

There were 18 reports of hepatic laboratory test alterations which were considered drug-related; nine reports of increased SGPT (0.62%), five reports of increased SGOT (0.34%), two reports of increased alkaline phosphatase (0.14%), and two reports of increased LDH (0.14%).

The kinds and incidence of adverse events rated as possibly drug-related or probably not drug-related were similar to those reported for definitely and probably related.

Most of the side effects reported during cefotetan teatment were mild in intensity, not clinically significant, and transient in nature. For the side effects considered related to cefotetan, treatment was stopped most frequently for hypersenitivity reactions (11 repoits) or gastrointestingal symptoms (5 repoits). See item C. for a detailed listing.

COMPARATIVE AGENTS

Summary information for patients treated with other cephalosporins is shown in Table 5 (cefoxitin), 6 (moxalactam) and 7 (cefotaxime). The most common drug-related side effects seen with cefoxitin were local reactions and hypersensitivity reastions; with moxalactam the most common reactions were changes in hemopoietic laboratory parameters. For the 19 patients who received cefotaxime, there was one drug-related reaction which was diarrhea.

CONCLUSION

In the population of 1451 patients treated with cefotetan, there were drug-related adverse signs and symptoms reported in a total of 4.6%. Where drug-related symptoms were reported, they were infrequent and generally mild in severity. The most frequently reported drug-related adverse sign and symptom was diarrhea, which was reported in 1.2% of all cefotetan-treated patients. Drug-related rash and SGPT increase were reported in 0.6% of the patients, eosinophilia in 0.5%, positive direct Coombs test in 0.4%, and thrombocytosis and SGOT increase in 0.3% of the cefotetan-treated patients. In only 11 patients, 0.8%, was cefotetan discontinued because of drug-related symptoms.

(2) Prophylaxis Studies

A total of 833 patients were given prophylaxis in the United States clinical trials: 497 with cefotetan, 170 with cefoxitin, and 166 with cefotaxime.

Adverse signs and symptoms definitely or probably related to the drug were reported in one cefotetan patient (0.2%) - hives; one cefoxitin patient (0.6%) - pruritis; and three cefotaxime patients (1.8%) - one rash and two reports of diarrhea.

TABLE 1

DEMOGRAPHIC DATA

DRUG TREATMENT GROUP	ALL PATIENTS					PATIENTS w/DRUG RELATED AS&S *				Total Drug Related AS&S
	Total	Male	Female	Mean Age (Range)	No Age Given	Total	Male	Female	Mean Age (Range)	
CEFOTETAN	1451	804	647	54 (16-100)	2	66	32	34	55 (19-94)	96
CEFOXITIN	233	162	71	61 (15-88)	1	5	2	3	48 (27-72)	7
MOXALACTAM	107	53	54	60 (19-91)	0	9	6	3	75 (64-86)	11
CEFOTAXIME	19	10	9	43 (20-93)	0	1	0	1	63 (63-63)	1
NO TREATMENT ADMINISTERED	6	2	4	43 (19-66)	0					
Totals:	1816	1031	785							

* Definitely and probably drug related

TABLE 2

AGE DISTRIBUTION OF PATIENTS BY YEARS

TREATMENT GROUP ===>	CEFOTETAN		CEFOXITIN		MOXALACTAM		CEFOTAXIME	
PATIENT STATUS ===>	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S
AGE GROUP:								
< 20	55	1	2	0	1	0	0	0
20 - 29	235	10	3	2	9	0	3	0
30 - 39	152	6	24	0	14	0	0	0
40 - 49	109	9	13	1	6	0	0	0
50 - 59	182	10	40	0	6	0	4	0
60 - 69	329	11	69	1	31	2	4	1
70 - 79	273	10	53	1	25	4	5	0
80 - 89	97	6	22	0	14	3	2	0
90 - 99	15	3	0	0	1	0	1	0
> 99	1	0	0	0	0	0	0	0
NO AGE GIVEN	2	0	1	0	0	0	0	0
	1451	66	233	5	107	9	19	1

TABLE 3

DRUG ADMINISTRATION: DOSAGE

TREATMENT GROUP ===>	CEFOTETAN		CEFOXITIN		MOXALACTAM		CEFOTAXIME	
PATIENT STATUS ===>	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S	ALL	WITH DRUG RELATED AS&S
DOSE AND FREQUENCY.								
0.5 GM Q6H	0	0	0	0	0	0	0	0
1.0 GM Q6H	1	0	0	0	0	0	10	0
1.5 GM Q6H	0	0	0	0	0	0	0	0
2.0 GM Q6H	0	0	0	0	0	0	7	1
2.5 GM Q6H	0	0	0	0	0	0	0	0
3.0 GM Q6H	0	0	0	0	0	0	0	0
0.5 GM Q8H	0	0	0	0	0	0	0	0
1.0 GM Q8H	1	0	191	5	46	5	1	0
1.5 GM Q8H	0	0	0	0	0	0	0	0
2.0 GM Q8H	0	0	42	0	46	3	0	0
2.5 GM Q8H	0	0	0	0	0	0	0	0
3.0 GM Q8H	0	0	0	0	2	0	0	0
0.5 GM Q12H	79	1	0	0	0	0	0	0
1.0 GM Q12H	375	12	0	0	0	0	0	0
1.5 GM Q12H	7	0	0	0	0	0	0	0
2.0 GM Q12H	702	41	0	0	12	1	1	0
2.5 GM Q12H	2	0	0	0	0	0	0	0
3.0 GM Q12H	176	9	0	0	1	0	0	0
0.5 GM Q24H	0	0	0	0	0	0	0	0
1.0 GM Q24H	82	1	0	0	0	0	0	0
1.5 GM Q24H	0	0	0	0	0	0	0	0
2.0 GM Q24H	25	2	0	0	0	0	0	0
2.5 GM Q24H	0	0	0	0	0	0	0	0
3.0 GM Q24H	0	0	0	0	0	0	0	0
	1451	66	233	5	107	9	19	1

TABLE 4

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: CEFOTETAN
NUMBER OF PATIENTS TREATED: 1451

APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP DOSE TMT	ADJ	OTHER
LOCAL EFFECTS																
INJECTION SITE - PHLEBITIS	5	0.34	4	1	0	5	0	4	0	1	0	0	3	0	0	2
INJECTION SITE - DISCOMFORT	3	0.21	2	1	0	3	0	3	0	0	0	0	3	0	0	0
INJECTION SITE - REDNESS	1	0.07	1	0	0	1	0	1	0	0	0	0	0	0	0	1
INJECTION SITE - SWELLING	1	0.07	1	0	0	1	0	1	0	0	0	0	1	0	0	0
CELLULITIS, FOREARM	1	0.07	1	0	0	1	0	1	0	0	0	0	1	0	0	0
SWELLING, FOREARM	1	0.07	1	0	0	1	0	1	0	0	0	0	1	0	0	0
			10	2	0	12	0	11	0	1	0	0	9	0	0	3
HYPERSENSITIVITY																
RASH	9	0.62	6	3	0	8	1	7	0	2	0	0	0	5	0	4
ITCHING	2	0.14	2	0	0	2	0	2	0	0	0	0	1	1	0	0
URTICARIA	1	0.07	0	0	1	0	1	1	0	0	0	0	0	1	0	0
ANGIONEUROTIC EDEMA	1	0.07	0	0	1	1	0	1	0	0	0	0	0	0	0	1
FEVER	1	0.07	0	1	0	1	0	1	0	0	0	0	0	1	0	0
CHILLS	1	0.07	1	0	0	1	0	1	0	0	0	0	0	1	0	0
PRURITUS	1	0.07	1	0	0	1	0	1	0	0	0	0	0	1	0	0
PAPULAR LESION	1	0.07	1	0	0	1	0	1	0	0	0	0	0	1	0	0
ERYTHEMA	1	0.07	1	0	0	1	0	1	0	0	0	0	1	0	0	0
			12	4	2	16	2	16	0	2	0	0	2	11	0	5

TABLE 4 (CONTINUED)

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: CEFOTETAN
APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP DOSE TMT	ADJ	OTHER
CARDIORESPIRATORY																
DYSPNEA	1	0.07	0	0	1	0	1	1	0	0	0	0	0	1	0	0
			0	0	1	0	1	1	0	0	0	0	0	1	0	0
GASTROINTESTINAL																
DIARRHEA	18	1.24	12	4	2	15	3	17	0	1	0	0	6	4	1	7
NAUSEA	2	0.14	0	0	2	0	2	1	0	1	0	0	0	1	1	0
VOMITING	1	0.07	0	0	1	0	1	0	0	1	0	0	0	0	1	0
			12	4	5	15	6	18	0	3	0	0	6	5	3	7
GENITOURINARY																
MONILIAL VAGINITIS	1	0.07	1	0	0	1	0	1	0	0	0	0	0	0	0	1
			1	0	0	1	0	1	0	0	0	0	0	0	0	1
MISC. CLINICAL																
BLISTERS IN MOUTH	2	0.14	2	0	0	2	0	2	0	0	0	0	0	0	0	2
SUBMANDIBULAR LYMPHADENOPATHY	1	0.07	0	1	0	1	0	1	0	0	0	0	0	1	0	0
SORE MOUTH	1	0.07	0	1	0	1	0	1	0	0	0	0	0	0	0	1
SORE THROAT	1	0.07	1	0	0	1	0	0	0	1	0	0	1	0	0	0
			3	2	0	5	0	4	0	1	0	0	1	1	0	3

TABLE 4 (CONTINUED)

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: CEFOTETAN
APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP TMT	DOSE ADJ	OTHER
HEMOPOIETIC																
EOSINOPHILS INCREASED	7	0.48	6	1	0	6	1	4	0	0	0	0	7	0	0	0
DIRECT COOMBS TEST POSITIVE	6	0.41	6	0	0	6	0	5	0	0	0	0	6	0	0	0
THROMBOCYTOSIS	5	0.34	4	0	0	5	0	4	0	0	0	0	5	0	0	0
PROTHROMBIN TIME INCREASED	1	0.07	0	0	0	0	1	1	0	0	0	0	1	0	0	0
NEUTROPENIA	1	0.07	0	0	0	1	0	1	0	0	0	0	1	0	0	0
			16	1	0	18	2	15	0	0	0	0	20	0	0	0
HEPATIC																
SGPT INCREASED	9	0.62	6	0	0	9	0	7	0	0	0	0	9	0	0	0
SGOT INCREASED	5	0.34	4	0	0	5	0	4	0	0	0	0	5	0	0	0
LDH INCREASED	2	0.14	2	0	0	2	0	2	0	0	0	0	2	0	0	0
ALK PHOS INCREASED	2	0.14	2	0	0	2	0	1	0	0	0	0	2	0	0	0
			16	0	0	18	0	14	0	0	0	0	18	0	0	0
TOTALS:	96		70	13	8	85	11	80	0	7	0	0	56	18	3	19

TABLE 5

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: CEFOXITIN
NUMBER OF PATIENTS TREATED: 233

APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP TMT	DOSE ADJ	OTHER
LOCAL EFFECTS																
INJECTION SITE - REDNESS	2	0.86	2	0	0	2	0	2	0	0	0	0	1	0	0	1
INJECTION SITE - DISCOMFORT	1	0.43	0	1	0	1	0	1	0	0	0	0	0	0	0	1
INJECTION SITE - SWELLING	1	0.43	1	0	0	1	0	1	0	0	0	0	0	0	0	1
			3	1	0	4	0	4	0	0	0	0	1	0	0	3
HYPERSENSITIVITY																
ITCHING	1	0.43	1	0	0	1	0	1	0	0	0	0	1	0	0	0
RASH WITH ITCHING	1	0.43	1	0	0	1	0	1	0	0	0	0	0	0	0	1
			2	0	0	2	0	2	0	0	0	0	1	0	0	1
CNS																
FLUSH	1	0.43	1	0	0	1	0	1	0	0	0	0	1	0	0	0
			1	0	0	1	0	1	0	0	0	0	1	0	0	0
TOTALS:	*** 7		*** 6	*** 1	*** 0	*** 7	*** 0	*** 7	*** 0	*** 0	*** 0	*** 0	*** 3	*** 0	*** 0	*** 4

TABLE 6

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: MOXALACTAM
NUMBER OF PATIENTS TREATED: 107

APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP TMT	DOSE ADJ	OTHER
HYPERSENSITIVITY																
RASH	1	0.93	0	1	0	0	1	1	0	0	0	0	1	0	0	0
			0	1	0	0	1	1	0	0	0	0	1	0	0	0
HEMOPOIETIC																
THROMBOCYTOSIS	3	2.80	3	0	0	3	0	0	0	0	0	0	0	0	0	0
PROTHROMBIN TIME INCREASED	2	1.87	1	1	0	0	2	2	0	0	0	0	1	1	0	0
DIRECT COOMBS TEST POSITIVE	2	1.87	2	0	0	1	1	1	0	0	0	0	1	0	0	1
			6	0	1	4	3	3	0	0	0	0	5	1	0	1
HEPATIC																
SGOT INCREASED	1	0.93	1	0	0	1	0	1	0	0	0	0	1	0	0	0
SGPT INCREASED	1	0.93	1	0	0	1	0	1	0	0	0	0	1	0	0	0
ALK PHOS INCREASED	1	0.93	1	0	0	1	0	1	0	0	0	0	1	0	0	0
			3	0	0	3	0	3	0	0	0	0	3	0	0	0
TOTALS:	*** 11		*** 9	*** 1	*** 1	*** 7	*** 4	*** 7	*** 0	*** 0	*** 0	*** 0	*** 9	*** 1	*** 0	*** 1

TABLE 7

ADVERSE SIGNS AND SYMPTOMS

TREATMENT GROUP: CEFOTAXIME
NUMBER OF PATIENTS TREATED: 19

APPRAISAL: DEFINITELY AND PROBABLY DRUG RELATED

BODY SYSTEM / ADVERSE SIGN AND SYMPTOM	NUMBER OF EVENTS	PERCENT OF PATIENTS TREATED	INTENSITY			SIGNIFICANT		OUTCOME TO DATE					ACTION TAKEN			
			MILD	MOD	SEV	NO	YES	RECOV	ALIVE UNDER W/SEQ	TMT	DIED	OTHER	NONE	STOP TMT	DOSE ADJ	OTHER
GASTROINTESTINAL																
DIARRHEA	1	5.26	1	0	0	1	0	0	0	0	0	0	0	0	0	0
	1		1	0	0	1	0	0	0	0	0	0	0	0	0	0
TOTALS	1		1	0	0	1	0	0	0	0	0	0	0	0	0	0

b. Deaths

There were 34 patient deaths reported in the original submission of January 20, 1984 (17 on cefotetan and 8 on comparative agents), and three patient deaths on cefotetan and two patients deaths on cefoxitin in the prophylaxis trials submitted on April 9, 1985.

None of the deaths were attributed to the study drug being used.

c. Discontinuations Due to an Adverse Sign or Symptom

Treatment was stopped most frequently for hypersenitivity reactions (11 reports) and gastrointestinal symptoms. Table 8 contains a detailed list of the patients discontinued.

TABLE 8

PATIENTS WHOSE THERAPY WAS DISCONTINUED
DUE TO AN ADVERSE SIGN AND SYMPTOM

TREATMENT GROUP: CEFOTETAN
APPRAISAL: DEFINITELY DRUG RELATED AND PROBABLY DRUG RELATED EVENTS

ADVERSE SIGN AND SYMPTOM	STUDY	PATIENT	AGE	SEX	INTENSITY	SIGNIFICANCE	DRUG RELATED	OUTCOME TO DATE
HYPERSENSITIVITY								
CHILLS	CEF 1-418-1	037	61	M	MILD	NO	PROBABLY	RECOVERED
FEVER	CEF 2-447-1	029	40	M	MODERATE	NO	DEFINITELY	RECOVERED
PRURITUS	CEF 2-460-1	024	54	M	MILD	NO	PROBABLY	RECOVERED
RASH	CEF 1-419-1	105	57	F	MODERATE	NO	PROBABLY	RECOVERED
	CEF 2-422-2	024	85	F	MILD	NO	PROBABLY	RECOVERED
	CEF 2-447-1	030	50	F	MILD	NO	DEFINITELY	RECOVERED
	CEF 2-460-1	024	54	M	MILD	NO	PROBABLY	RECOVERED
	CEF 2-470-1	023	74	M	MILD	YES	PROBABLY	RECOVERED
URTICARIA	CEF 2-434-1	007	35	F	SEVERE	YES	DEFINITELY	RECOVERED
ITCHING	CEF 2-438-1	020	19	F	MILD	NO	PROBABLY	RECOVERED
PAPULAR LESION	CEF 2-438-1	020	19	F	MILD	NO	PROBABLY	RECOVERED
CARDIORESPIRATORY								
DYSPNEA	CEF 2-434-1	007	35	F	SEVERE	YES	DEFINITELY	RECOVERED
GASTROINTESTINAL								
DIARRHEA	CEF 1-419-1	105	57	F	MILD	NO	PROBABLY	RECOVERED
	CEF 1-419-1	306	67	F	MILD	NO	PROBABLY	RECOVERED
	CEF 1-419-1	322	24	F	MILD	NO	PROBABLY	RECOVERED
	CEF 2-470-1	023	74	M	MILD	YES	PROBABLY	RECOVERED
NAUSEA	CEF 2-434-1	007	35	F	SEVERE	YES	DEFINITELY	RECOVERED
MISC. CLINICAL								
SUBMANDIBULAR LYMPHADENOPATHY	CEF 2-447-1	029	40	M	MODERATE	NO	PROBABLY	RECOVERED

TABLE 8 (CONTINUED)

PATIENTS WHOSE THERAPY WAS DISCONTINUED
DUE TO AN ADVERSE SIGN AND SYMPTOM

TREATMENT GROUP: MOXALACTAM
APPRAISAL: DEFINITELY DRUG RELATED AND PROBABLY DRUG RELATED EVENTS

ADVERSE SIGN AND SYMPTOM	STUDY	PATIENT	AGE	SEX	INTENSITY	SIGNIFICANCE	DRUG RELATED	OUTCOME TO DATE
HEMOPOIETIC								
PROTHROMBIN TIME INCREASED	CEF 3-502-1	009	86	F	SEVERE	YES	PROBABLY	RECOVERED

2. Efficacy

Table A
Cefotetan
Bacteriologic Response by Pathogen
All Evaluable Patients
(Eradicated/Total Infections - %)
* = claim granted

Predominate Organisms Evaluated	Urinary Tract	Lower Respiratory Tract	Skin and Skin Structure	Gynecologic	Intra-Abdominal	Bone Joint
E. coli	*265/284 93%	*21/21 100%	*14/17 82%	*19/20 95%	7/8 88%	
Enterobacter sp.	9/9 100	13/16 81%	7/8 88	5/5	1/1	
Haemophilus sp.		4/4		9/10 90		
H. influenzae		*41/47 87				
Klebsiella sp.	*11/14 79	*12/13 92	2/2			
Klebsiella pneumoniae	*53/55 97	*17/19 90	3/3	4/5	2/2	2/2
Neisseria gonorrhea				*28/29 97		
Proteus, indole pos	*11/11 100		7/7		1/1	
Proteus mirabilis	*58/62 94	6/6 100	13/17 76	*12/12 100	2/2	
Staph aureus	2/2	*19/19 100	*93/98 95	6/6 100	1/1	*8/8
Staph epidermidis	3/3		*16/19 84	*16/16 100	1/1	
Streptococcus sp.	1/3	6/6 100	*21/22 95	*28/30 93	3/3	1/1
Strep agalactiae			7/8 88	*16/17 94		1/1
Strep pneumoniae		*41/51 80				
Strep pyogenes			*38/38 100	5/5		2/2

Table A. (Cont'd)

Predominate Organisms Evaluated	Urinary Tract	Lower Respiratory Tract	Skin and Skin Structure	Gynecologic	Intra-Abdominal
Acinetobacter sp.				1/1	
Bacteroides sp.			3/4	10/13	
Bacteroides bivius				8/9	
B. fragilis			4/6	2/2	3/3
B. melaninogenicus			3/3	5/5	
Citrobacter sp.	3/5	4/6	2/3	2/2	
Clostridium sp.				2/2	3/3
Corynebacterium sp.				1/1	
Diptheroids	1/1		1/1		
Enterococcus			3/6	7/7	2/2
Eubacterium sp.				1/1	
Fusobacterium sp.			1/1	7/7	
Lactobacillus sp.	0/1				
Pasturella sp.			1/1		
Peptococcus sp.			3/4	8/8	
Peptostreptococcus sp.			3/3	3/3	
Propionibacterium sp.			1/1		
Pseudomonas sp.		2/2	1/1		
Ps. aeruginosa	1/1				
Salmonella sp.			1/1		
Serratia marcescens	0/1	8/9	2/3		
Veillonella sp.			1/1		2/3
Other anaerobes			2/7		9/9
Other gram neg.			3/3		

VI. Conclusions

The controlled and uncontrolled studies submitted and reviewed have demonstrated that cefotetan is safe and effective for the treatment of the following infections when caused by susceptible strains of the designated organisms.

URINARY TRACT INFECTIONS caused by E. coli, Klebsiella species (including K. pneumoniae), Proteus mirabilis, Proteus vulgaris, Providencia rettgeri (formerly Proteus rettgeri) and Morganella morganii (formerly Proteus morganii).

LOWER RESPIRATORY TRACT INFECTIONS caused by Streptococcus pneumoniae (formerly D. pneumoniae), Staphylococcus aureus (penicillinase and non-penicillinase producing), Haemophilus influenzae (including ampicillin resitant strains), Klebsiella species (including K. pneumoniae), and E. coli.

SKIN AND SKIN STRUCTURE INFECTIONS caused by Staphylococcus aureus (penicillinase and non-penicillinase producing), Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus species (excluding enterococci), and E. coli.

GYNECOLOGIC INFECTIONS caused by Staphylococcus epidermidis, Streptococcus species (excluding enterococci), E. coli, Proteus mirabilis, and Neisseria gonorrhaeae.

BONE AND JOINT INFECTIONS caused by Staphylococcus aureus.

PROPHYLAXIS

The preoperative administration of a single dose of cefotetan may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaiminated (e.g cesarean section, abdominal or vaginal hysterectomy, and transurethral surgery).

VII. Recommendations:

1. It is recommended on the basis of the clinical data contained in Antibiotic Form 5 50-588 that cefotetan be found approvable as safe and effective for the indications listed under conclusions.

[illegible] with Stuart
[illegible] labeling.

[illegible]
[illegible] Stanley, M.D.

cc:
Orig Form 5
HFN-340
HFN-815
HFN-239
HFN-815/CSO
HFN-815/GStanley:bam:6/8/85
4141b

Form 5 50-508

CEFOTETAN
7/20/88

Medical Officer's Review and Evaluation of an Amendment (HOR #2)

Amendment dated: June 24, 1985
Received by reviewer: June 25, 1985
Review completed: July 17, 1935

Reason for amendment: To expand data on which to base claims for Proteus mirabilis, Enterobacter species, Streptococcus species, anaerobes, and surgical prophylaxis.

Sponsor: Stuart Pharmaceuticals
Division of ICI Americas Inc.
Wilmington, Delaware 19897

Drug Name: trade: Apacef
generic: cefotetan disodium for injection

Background:

On June 14, 1985, Dr. James King and I met with representatives of Stuart Pharmaceuticals to discuss the findings of our completed reviews and to go over line by line their proposed labeling for cefotetan.

The company representatives were told the following at that time.

1. An intra-abdominal claim for the use of cefotetan could not be granted because 7/8 E. coli infections cured was too low a number of infections on which to base an entire claim.

2. A cure rate of 76% (13/17 infections) for Proteus mirabilis skin and skin structure infections was too low a cure rate on which to base a claim when four recently approved cephalosporins cured 91%, 98%, 100%, and 91% of infections treated.

3. Too few anaerobic infections had been treated to grant any anaerobic claim for any organ system.

4. It was doubtful that any Enterobacter species claim would be granted because greater than 50% of Enterobacter species tested were resistant to cefotetan and granting a claim was felt to infer that a physician had better than a 50-50 chance of curing an infection. The topic was to be discussed at the next Medical Officers' meeting.

5. The carcinogenesis, mutagenesis statement concerning testicular toxicity had been referred to Mr. Jack Davitt for review.

Data submitted

One volume containing tabular summaries of additional patients treated, and summaries of these additional patients and summaries of the total results from the previous submissions plus this submission are submitted in support of the following claims.

1. Enterobacter species in urinary tract and respiratory tract infections.

2. Proteus mirabilis skin and skin structure infections.

3. Anaerobic gynecologic and intra-abdominal infections.

4. Streptococcus species intra-abdominal infections.

5. Additional cases supporting use in surgical prophylaxis.

Clinical Review

a. Intra-abdominal infections

Additional evaluable cases are submitted for nine cefotetan treated and 2 moxalactam treated patients.

These acceptable cases, when added to the previously reviewed cases, provide the results listed in Tables 1 and 2.

It can be concluded from these tables that cefotetan is as effective as moxalactam in the treatment of Escherichia coli intra-abdominal infections. Additionally, cefotetan is demonstrated to be effective in the treatment of intra-abdominal infections caused by Streptococcus species (excluding enterococci), and Bacteroides species (excluding B. distasonis, B. ovatus, and B. thetaiotaomicron).

Table 1. Total Evaluable Intra-Abdominal Cases (as of 6/17/85)
Bacteriological Response by Pathogen for Patients Treated with Cefotetan

Pathogens	Number of Isolates: Single Organism Infection	Polymicrobial Infection	Total	Bacteriological Response: Satisfactory*	Unsatisfactory
S. aureus	0	2	2	2	0
S. epidermidis	1	2	3	3	0
Streptococcus viridans	0	1	1	1	0
Streptococcus, Group D	0	5	5	5	0
Streptococcus sp.	0	13	13	13	0
Enterococcus	0	2	2	2	0
Lactobacillus bulgaricus	0	1	1	1	0
E. coli	10	27	37	36	1
Klebsiella pneumoniae	2	5	7	7	0
Klebsiella sp.	0	3	3	3	0
P. mirabilis	1	3	4	4	0
Proteus indole - positive	0	1	1	1	0
Haemophilus parainfluenzae	0	1	1	1	0
Enterobacter aerogenes	0	1	1	1	0
Enterobacter sp.	0	5	5	5	0
Eikenella corrodens	0	1	1	1	0
Citrobacter freundii	0	1	1	1	0
Pseudomonas aeruginosa	0	1	1	1	0
Pseudomonas fluorescens	0	2	2	2	0
Pseudomonas sp.	1	0	1	1	0
Acro hydrophilia	1	0	1	1	0
Other gram negative	0	1	1	1	0
B. fragilis	1	4	5	5	0
Bacteroides sp.	0	15	15	15	0
Clostridium sp.	0	6	6	6	0
Bifidobacterium animalis	0	1	1	1	0
Eubacterium lentum	0	2	2	2	0
Fusobacterium mortiferum, varium	0	1	1	1	0
Peptococcus sp.	0	2	2	2	0
Peptostreptococcus sp.	0	3	3	3	0

*Includes patients in whom there was no material to culture because of clinical improvement
* = additional claims granted

Table 2. Total Evaluable Intra-Abdominal Cases (as of 6/17/85)
Bacteriologic Response by Pathogen for Patients Treated with Moxalactam

Pathogen	Number of Isolates: Single Organism Infection	Polymicrobial Infection	Total	Bacteriologic Response: Satisfactory*	Unsatisfactory
Micrococcus species	0	1	1	1	0
Streptococcus, Group F	0	1	1	1	0
Alpha-hemolytic Streptococcus	1	1	2	2	0
Non-hemolytic Streptococcus	0	2	2	2	0
Streptococcus, Group B	0	1	1	1	0
Streptococcus species	2	0	2	2	0
Streptococcus, Group D (Non-enterococcus)	1	0	1	1	0
Escherichia coli	1	8	9	8	1
Klebsiella corrodens	0	3	3	3	0
Enterobacter aerogenes	0	1	1	1	0
Klebsiella pneumoniae	0	1	1	1	0
Klebsiella species	1	2	3	2	1
Proteus mirabilis	2	1	3	2	1
Pseudomonas aeruginosa	0	2	2	2	0
Bacteroides distasonis	0	2	2	2	0
Bacteroides fragilis	0	2	2	2	0
Bacteroides oralis	0	1	1	1	0
Bacteroides ovatus	0	1	1	1	0
Bacteroides ureolyticus	0	1	1	1	0
Bacteroides vulgatus	0	1	1	1	0
Clostridium pseudotetanicum	0	1	1	1	0
Clostridium species	0	1	1	1	0
Eubacterium lentum	0	1	1	1	0
Fusobacterium mortiferum, varium	0	1	1	1	0
Peptococcus asaccharolytics	0	2	2	2	0
Peptococcus magnus	0	1	1	1	0
Peptostreptococcus micros	0	1	1	1	0
Peptostreptococcus productus	0	1	1	1	0
Peptostreptococcus species	0	1	1	1	0

*Includes patients in whom there was no material to culture because of clinical improvement

b. Gynecologic Infections

Data from twenty-five additional evaluable patients treated with cefotetan gynecologic infections is submitted.

These acceptable cases, when added to the previously reviewed cases, provide the data displayed in Table 3.

Claims for E. coli, Neisseria gonorrhoae, Proteus mirabilis, Staphylococcus epidermidis, and Streptococcus species were granted in the previous review. It is concluded from the expanded data that cefotetan is also effective in gynecologic infections caused by Bacteroides species (excluding B. distasonis, B. ovatus, and B. thetaiotaomicron) and Fusobacterium species, and Gram positive anaerobes including Peptococcus and Peptostreptococcus species.

Table 3. Total Evaluable Gynecologic Cases (as of 6/17/88)
Bacteriological Response by Pathogen for Patients Treated with Cefoxitin

Pathogens	Number of Isolates: Single Organism Infection	Polymicrobial Infection	Total	Bacteriological Response: Satisfactory*	Unsatisfactory
S. aureus	2	7	9	9	0
S. epidermidis	1	18	19	19	0
Str. pyogenes	3	3	6	6	0
Str. agalactiae	7	18	25	24	1
Streptococcus sp.	7	30	37	36	2
Enterococcus	0	7	7	7	0
Corynebacterium sp.	0	1	1	1	0
Bacillus sp.	2	0	2	2	0
Diphtheroids	0	2	2	2	0
E. coli	6	26	32	31	1
K. pneumoniae	2	5	7	6	1
Enterobacter sp.	0	6	6	6	0
P. mirabilis	3	9	12	12	0
Proteus indole pos.	1	0	1	1	0
Citrobacter sp.	2	0	2	2	0
Haemophilus sp.	3	9	12	11	1
N. gonorrhoea	26	22	48	47	1
Acinetobacter var anitratus	0	1	1	1	0
B. fragilis	0	3	3	3	0
B. melaninogenicus	1	6	7	7	0
B. bivius	0	9	9	8	1
Bacteroides sp.	0	16	15	13	2
Fusobacterium sp.	1	6	7	7	0
Clostridium sp.	0	3	3	3	0
Eubacterium sp.	0	1	1	1	0
Peptococcus sp.	1	9	10	10	0
Peptostreptococcus sp.	0	5	5	5	0
Veillonella sp.	0	3	3	2	1
Other anaerobes	2	6	8	8	0

*Includes patients in whom there was no material to culture because of clinical improvement

* = additional claims granted

c. Proteus mirabilis skin and skin structure infections

In my MOR #1 dated May 23, 1985, I denied a claim for Proteus mirabilis skin and skin structure infections based on the fact that cefotetan cured only 13/17 (76%) infections treated, despite curing 58/62 Proteus mirabilis UTI's and 12/12 gynecologic infections. The reason for this high failure rate is not apparent.

This amendment submits data from 14 additional evaluable cases. 9/13 of these cases were cured bringing the overall cure rate for Proteus mirabilis skin and skin structure infections treated with cefotetan to 22/30 (73%).

When one considers that the cure rates in Proteus mirabilis skin and skin structure infections for five recently approved cephalosporins were the following:

cefoxitin	21/23	91%
cefotaxime	40/41	98%
ceftizoxime	27/27	100%
ceftriaxone	29/32	91%

it is felt that this low cure rate is unacceptable and the claim is therefore not granted.

d. Enterobacter urinary tract and respiratory tract infections

In my MOR #1 I denied any claims for enterobacter based on the fact that over 50% of enterobacter strains tested in the studies submitted were resistant to cefotetan. The data originally submitted demonstrated a cure rate in Enterobacter sp. infections of 9/9 urinary tract infections and 13/16 (81%) lower respiratory tract infections. By stipulation of the protocols used, therapy could only be continued in patients whose organisms were sensitive to cefotetan, and in the above infections the Enterobacter species isolated were sensitive to cefotetan in vitro (ie. part of the approximately 45% of Enterobacter species tested that were sensitive to cefotetan).

The company felt that my position was unduly rigorous and that the claim should be granted. I proposed to discuss the issue with all other medical officers in the Division and this was done at the Medical Officers' Meeting of June 19, 1985. The unanimous consensus after an hour's discussion was that we should not give clinical claims for organisms when approximately 40% or more of organisms tested are resistant to the antibiotic under study, particularly when excellent alternatives are available, since such clinical claims are perceived by practicing physicians as a reasonable guarantee that the antibiotic will be effective for the claim granted.

Accordingly, all claims for Enterobacter species are denied.

e. Surgical Prophylaxis

The company has submitted the following additional acceptable cases in support of use as surgical prophylaxis.

Colorectal surgery	- 12 cefotetan,	5 cefoxitin
Appendiceal surgery	- 3 cefotetan,	1 cefoxitin
Upper GI surgery	- 2 cefotetan,	1 cefoxitin, 2 cefotaxime
Biliary tract surgery	- 10 cefotetan,	6 cefoxitin

When these additional cases are added to those already found acceptable, the following results are obtained.

In biliary tract surgery 38/43 (88.4%) patients receiving cefotetan prophylaxis and 20/22 (90.9%) patients receiving cefotaxime prophylaxis had a successful outcome (no infections, no febrile morbidity).

In gastrointestinal tract surgery (the claim that has been granted to other cephalosporins) the results were as follows.

Cefotetan had a successful outcome (no infection, no febrile morbidity) in 41/55 (75%) of cases given prophylaxis as compared with 20/28 (72%) cases given prophylaxis with an approved comparative antibiotic (25 cefoxitin, 3 cefotaxime).

The numbers of patients studied and the results are similar to those for antibiotics previously granted surgical prophylaxis claims and the claims of biliary tract and gastrointestinal tract surgical prophylaxis are therefore granted.

f. Efficacy based on a limited number of organisms studied.

The conclusion of the Medical Officers' meeting on July 17, 1985, was that when one considers the MIC's of a particular antibiotic, the tissue levels achieved, the frequency of occurrence of the particular infection, the number of organisms studied and the cure rates for both the organism and the body system under consideration, that it is often appropriate to award claims based on less than ten organisms studied for a particular infection in a specific organ system. It was felt that this overall appraisal should be left to the medical officer.

It was also concluded that when such claims are granted, they should be marked with an asterisk and the following foot note added - "*Efficacy for this organism in this organ system was studied in less than 10 infections."

Accordingly, the following claims should be added to the Indications section for cefotetan:

Gynecologic infections caused by Staphylo[illegible]s aureus (9/9 cured).
Intra-abdominal infections caused by Klebsiella species including Klebsiella pneumoniae (7/7 pneumonia, 3/3 species cured).

Overall Conclusions

Based on the data submitted in the amendment and the previous submissions to this NDA, the following conclusions are reached.

1. No claim should be granted for the use of cefotetan in the treatment of urinary tract and respiratory tract infections caused by Enterobacter species because of the resistance problem with enterobacter.

2. No claim should be granted for the use of cefotetan in the treatment of Proteus mirabilis skin and skin structure infections because of the poor cure rate - 13/17 (76%).

3. Based on the data submitted for intra-abdominal infections, cefotetan is found (in addition to the claims granted in NOR #1) to be effective in infections caused by Klebsiella species including K. pneumoniae, Streptococcus species (excluding enterococci) and Bacteroides species (excluding B. distasonis, B. ovatus, B. thetaiotaomicron). E. coli missing

4. Based on the data submitted for gynecologic infections, cefotetan is found to also be effective in infections caused by Staphylococcus aureus*, Bacteroides species (excluding B. distasonis, B. ovatus, and B. thetaiotaomicron), Fusobacterium species*, and Gram positive anaerobes including Peptococcus and Peptostreptococcus* species.

   Immediately following Bone and Joint Infections in the Indications section, the sponsor should add the following statement:

   *Efficacy for this organism in this organ system was studied in less than 10 infections.

5. Based on the data submitted for surgical prophylaxis, cefotetan has been demonstrated to be as effective as the approved comparative antibiotics studied in reducing infections and infectious morbidity in gastrointestinal tract surgery and biliary tract surgery.

6. Mr. Davitt is completing the preferred wording for the testicular toxicity statement. Dr. King and I have gone over the final labeling for cefotetan over the telephone with representatives of Stuart. We are in agreement on the wording for the final printed labeling.

Recommendation:

It is recommended that cefotetan be approved for the claims which were found approvable in MOR #1 dated May 23, 1985, and in this amendment.

George R. Stanley, M.D.

cc:
Orig Form 5
HFN-235
HFN-340
HFN-815
HFN-815/CSO
HFN-815/JDavitt
HFN-815/GRStanley:bam:7/19/85
0079m

Form 5 50-588

Medical Officer's Review #3 - Review of Final Printed Labeling

Submission dated: August 9, 1985
Received by reviewer: September 10, 1985
Review completed: September 11, 1985

Sponsor: Stuart Pharmaceuticals
Wilmington, Delaware 19897

Drug name: generic: Cefotetan disodium for injection

Trade: Cefotan

Reason for submission: Final printed labeling.

Clinical Review:

Dr. James King, microbiologist, and I have reviewed the labeling and have the following recommendations:

The labeling, as submitted, will be acceptable when the following changes are made:

Under

INDICATIONS AND USAGE

TREATMENT

When the name of an organism is abbreviated, a period should follow the abbreviated word - i.e. E. Coli, not E Coli

The following changes should also be made.

Gynecologic Infections

An asterisk should be added after Staphylococcus aureus*, and the asterisk presently following 'eptostreptococcus species* should be changed to Peptostreptococcus* species.

Intra-abdominal Infections

An asterisk should be added following K. pneumoniae*

Bone and Joint Infections

An asterisk should be added following Staphylococcus aureus*

In the statement "*Efficacy for this organism in this organ system was studied in less than ten infections.", the word less should be changed to fewer.

Conclusions:

1. It is recommended that the Form 5 for cefotetan be approved, provided the sponsor makes the above recommended changes in labeling prior to marketing the drug.

2. The Drug Monograph for cefotetan is not yet completed. If it is not completed by the completion of HFN-800 review, an approvable, rather than an approval, letter will have to be issued.

George R. Stanley, M.D.
Group Leader, DAIDP

cc:
Orig Form 5
HFN-815 ST 9/30/85
HFN-815/CSO
HFN-815/RNorton
HFN-815/GRStanley:llm/9/12/85
0228m

Chem Rev

30

DRUG CONTROL REVIEW NOTES

1. TYPE ☒ IND ☐ A

2. NO. 50-588

3. SPONSOR
Stuart Pharmaceuticals,
Division of ICI Americas, Inc. Attn: Allan J. Milbauer

4. ADDRESS
Concord Pike & New Murphy Road,
Wilmington, DE 19897

5. SUBMISSIONS REVIEWED

a. ORIGINAL DATED
Jan. 20, 1984

b. AMENDMENTS DATED
April 6, 1984
April 16, 1984

5c. PROVIDING FOR
1. Changes in sample preparation for dosage forms; exhibit samples.
2. Revision of GC for residual solvents.

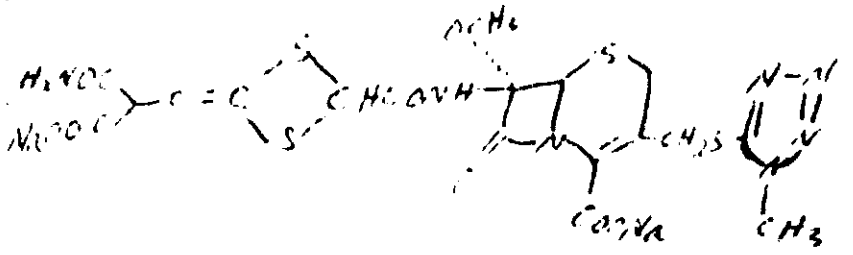
6. a. TRADE
Apacef

b. NON-PROPRIETARY
cefotetan disodium for injection

c. CHEMICAL
[6R-(6α,7β)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidine)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, sodium salt.

d. ESTAB
none designated

7. STRUCTURAL FORMULA



Injectable
0.5, 1.0, & 2.0 g. vials and
1.0 & 2.0 g. bottles.

X cephalosporin antibiotic

[redacted]

See attached comments

13. CONCLUSIONS
The manufacturing and controls will be satisfactory when an acceptable CGMP evaluation is received from Compliance, the draft certification monographs are negotiated, and satisfactory draft labeling has been filed. The firm was notified of labeling deficiencies in a telephone conversation dated 5/23/84.

14. DATE REVIEWED	15. REVIEWER	
May 23, 1984	James R. King	James R. King 5/23/84

FORM FDA 1313 COPY TO: DIVISION IND HFN-815, HFN-815/CSO, HFN-178

NDA

50588

PHARM

REV

Enq. 1/6/85

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-588 (Original Submission, dated 1/31/84)

Date Review Completed: 8/2/84

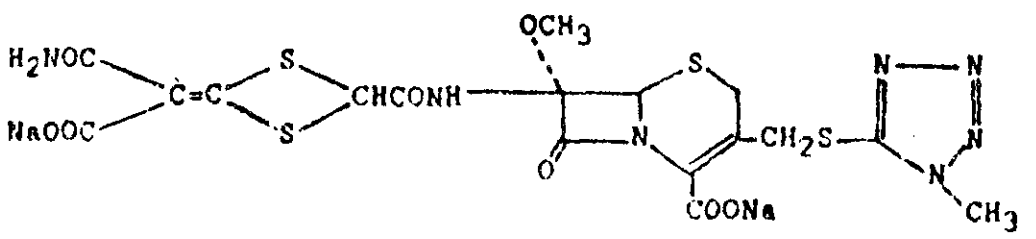
Applicant: Stuart Pharmaceuticals (Div. of ICI Americas), Wilmington, Del.

Drug: APACEF™ (cefotetan disodium) for injection

Code Name: ICI 156,384 (Japan); YM09330 (UK)

Category: Antibiotic ("cephamycin")

Chemical Structure:



Dosage Form: Lyophilized Injectable for IM or IV admin.

Related Submission: [redacted]

Drug Source: Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

Dosage & Admin.: The usual adult dosage (it is not administered to children) is 1 or 2gm (80mpk/50kg adult) administered IV or IM, q 12 h for 5-10 days. For life-threatening situations, a daily dose of 6gm (3g q 12 h, or 120mpk/50kg adult) can be administered. This is the maximum daily dose and should not be exceeded.

APACEF™ is supplied as a powder in vials containing cefotetan disodium equivalent to 500mg, 1gm & 2gm cefotetan activity for IV & IM administration.

The following animal studies are new and have not been previously reviewed. Unless otherwise designated, these experiments were performed by the Yamanouchi Pharmaceutical Co., Ltd.

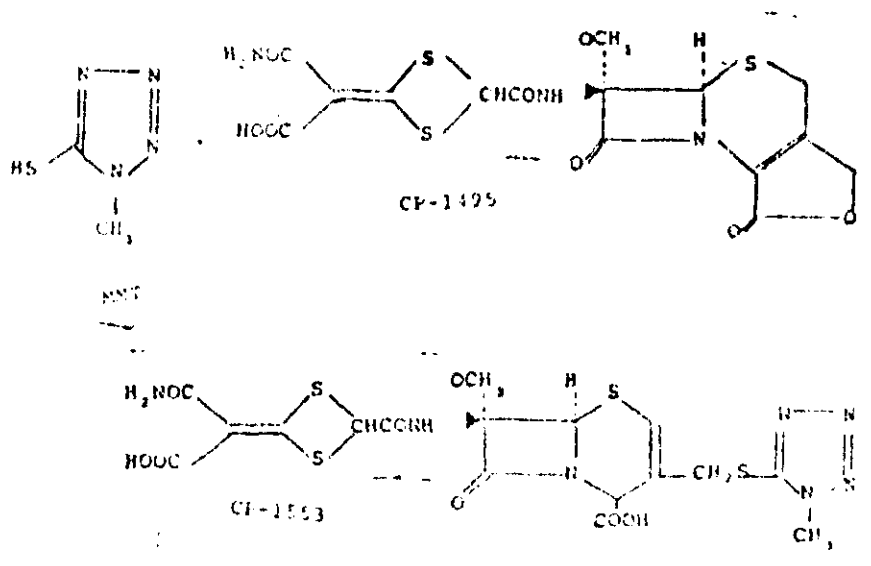
ACUTE TOXICITY

A. Acute Intravenous Study in the Rat

Compound	Sex	LD_{50} (mg/kg)	95% Conf. Limit
Degraded preparation	M	6.58	(6.16-7.03)
	F	5.58	(5.23-5.97)
Degraded 25% sol'n	M	7.35	(6.88-7.85)
	F	6.18	(5.73-6.66)
Tetrazol (MMT)	M	2.37	(2.21-2.54)
	F	2.34	(2.19-2.49)
CP-1495	M	>1.00	
	F	>1.00	
CP-1553	M	>1.00	
	F	>2.00	

Observations: "Toxic signs observed after administration of two kinds of degradation products were the same as those observed in mice given YM09330.

Similar toxic symptoms were seen, but to a lesser extent, in animals which received tetrazol." Almost all animals receiving CP-1495 & C-1553 exhibited decreased locomotor activity and mild bradypnea.



Note: MMT, CP-1495 & CP-1553 are minor components of cefotetan disodium and are less than 1% of the drug.

B. Acute Subnephrocapsular Study

In a previous acute study in mice subnephrocapsular hemorrhage occurred with cefotetan admin. The purpose of this experiment was to determine if this effect was found in similar compounds, or peculiar to cefotetan only. The following 7 were tested: cefmetazole (CMZ), cefazolin (CEZ), cephalothin (CET), cefoperazone (T-1551), latamoxef (6059-S), carbenicillin (CBPC) & sulbenicillin (SBPC). The Na salts were used in all cases.

Procedure: F mice, 10/group, were IV administered 5g/kg (T-1551, 4g/kg) or saline (N, 6%).

Results: Subnephrocapsular hemorrhage occurred with the following preparations: cefotetan, 60595, CBPC & SBPC.

The investigators concluded that subnephrocapsular hemorrhage is not specific to only cefotetan disodium, but also to B-lactam antibiotics (disodium salts) which dissociate to divalent radicals.

SUBACUTE TOXICITY

A. 5-Week Intraperitoneal Study of MMT in the Rat

Procedure: Male rats (SD CRJ-CD strain) Charles River, Japan, were divided into 3 groups (12/gp) and IP administered MMT (a minor component of CFT) at 0, 5 & 100mpk, which corresponds to 500-1000mpk of cefotetan disodium (LD) and "a 20x higher dosage" of the HD. Half the animals were treated for 3 wks, the other half for 5 wks. The animals were killed at the above time periods and necropsies performed.

Results:

1. There were no deaths or abnormal clinical signs.

2. Body wt gain was reduced in HD beginning day 10.

3. Hematology was normal (PCV only was tested).

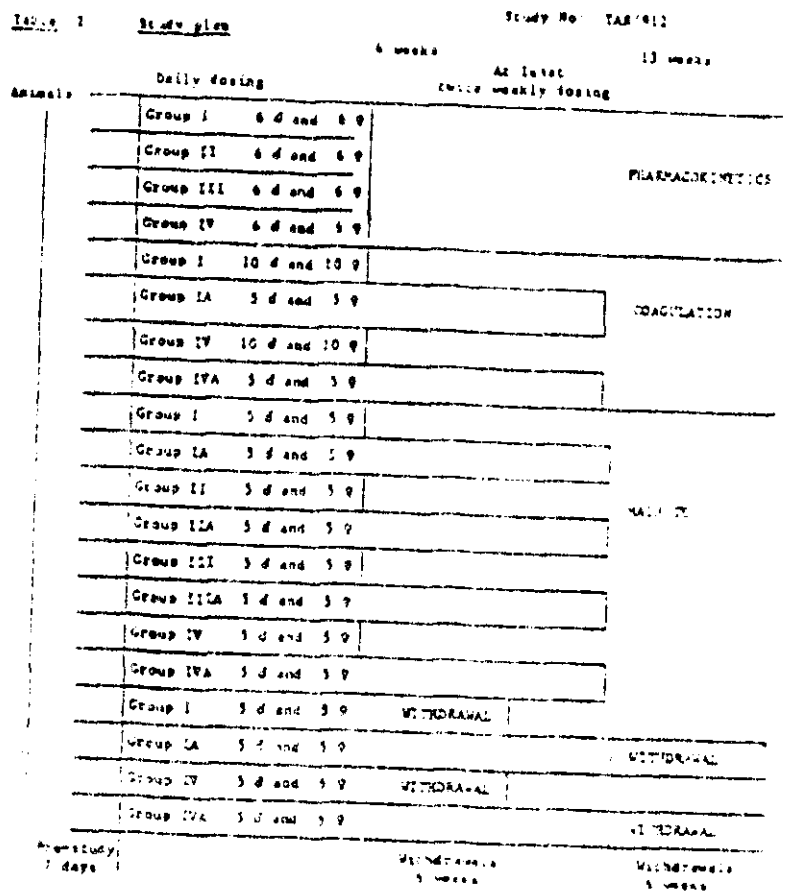
4. Three week rats showed decreases in triglycerides and phospholipids (HD). Five week rats showed decreases in triglycerides & alkaline phosphatase (HD).

5. Rel. & abs. liver & kidney wts were comparable to controls.

6. Histopathology: "Fibrosis occurred in the parietal peritoneum and the visceral peritoneum of the liver and its surrounding organs." The parenchymal areas of these organs were not affected. These changes are ascribed to the local irritation of the drug.

B. Three-month Intramuscular Study in Rat (ICI-UK)

The design of this experiment can be somewhat confusing and is easiest to understand by including the following tables taken from the submission.



ZD6126

Group I (Control):	0	mg/kg/day :	26 ♂ and 26 ♀	)
IA	0	mg/kg/day :	15 ♂ and 15 ♀	)
II	100	mg/kg/day :	11 ♂ and 11 ♀	) - DOSING FOR 1 MONTH
IIA	100	mg/kg/day :	5 ♂ and 5 ♀	)
III	200	mg/kg/day :	11 ♂ and 11 ♀	) NB Groups IA, IIA, IIIA
IIIA	200	mg/kg/day :	5 ♂ and 5 ♀	) and IVA dosed at least
IV	250	mg/kg/day :	26 ♂ and 26 ♀	) twice weekly until the
IVA	250	mg/kg/day :	15 ♂ and 15 ♀	) 1 month interim kill
			114 ♂ and 114 ♀	)

The unique ICI animal identification numbers to be used in this study are shown in Appendix V.

Additional Information:

1. The active material was dissolved in 0.5% aq. lignocaine.

2. "All rats were injected daily into the musculature...up to a limit of 0.2ml/animal. When this limiting volume of injection was reached for each animal (200g body wt) the remainder of the dose was given intraperitoneally..."

3. The Gps I, II, III & IV animals were killed after 28-32 days of dosing. The Gps IA, IIA, IIIA or IVA were injected for 13 wks (84-88 days).

4. Additionally, 5/sex rats in each of Gps I, IV, IA & IVA were dosed at the same time as the main test gps for 1 mo. & 3 mos. with each treatment period followed by a 6-wk withdrawal period before necropsy.

Mortality: None

Food Consumption: Normal

Body Wt Gain: Decreased in M of Gp III & IV beginning about the 7th & 8th wks, respectively

Ophthalmological Exam: Normal

Blood Pressure, Heart Rate, Body Temp: Normal

Hematology: At 12 wks, gp IVA showed reduced Hb, RBC & PCV values.

Clinical Chemistry: No sig. findings

Urinalysis: Decreased Na values were seen in the 3-mo. treated gps at 4 & 12 wks; also in the 1-month animals at days 9 & 23. This was not seen in the reversible gp.

Organ Weights: Relative liver wts were reduced in all 1 & 3-month treated gps, except Gp IVA F. The reversible groups were normal except for Gp IV F, which showed a reduced rel. liver wt. Liver (abs.) wts were also reduced in many of the 1 & 3-month treated gps.

Gross Pathology: (I, IA, IV & IVA main & withdrawal gps): All the treated animals, with 1 exception (1 Gp 3 F) showed distended ceca - a common finding with antibiotic treatment. The control and withdrawal gps did not show extended ceca.

Histopathology: Related to the local effects of the drug and/or its vehicle at the injection sites were hemorrhage, siderosis & chronic inflammatory cell infiltration. Also, an "increased incidence of bruising in GP IV & IVA may be related to the increased viscosity of the dosing solution at higher dose levels."

Pharmacokinetic Studies: The following was obtained from the gps from which blood was obtained at 28 days.

1. Plasma conc'ns were linear to dose levels.

2. Half-life of the test formulation was 24 min. (0.25-2 hrs).

3. Highest conc'ns were detected at 15 min. post-dose.

C. 28-Day Cefotetan-Gentamicin Intravenous Study in Rats (ICI-UK)

Study Design:		No. of Animals		
		1 Month	+ 6-wk w'draval	Dose Levels (mpk)
Group:	I	5/sex	5/sex	0 (saline)
	II	"	0	20 (gentamicin)
	III	"	0	40 (gentamicin)
	IV	"	0	100 (cefotetan)
	V	"	5/sex	100 + 20 (cefot. + gent.)
	VI	"	5/sex	100 + 40 (" " ")

Note: Circumstances may arise where gentamicin, a nephrotoxic drug, may be used in conjunction with cefotetan. Is this nephrotoxicity enhanced when the two are administered together?

Route & Duration: Cefotetan was IV administered up to day 10. "As a result of difficulties experienced in multiple dosing, the route of administration was changed to intraperitoneal for the remainder of the study - 28 days." (Difficulties experienced were cyanosis of tails & difficulty in injecting into the tail vein.) "Previous pharmacokinetic studies....indicated very little difference in bioavailability with either route."

Mortality: None

Food Intake; Body Wt Gain; Ophthalmological Exam: Normal

Water Intake: Increased in treated gps; normal in withdrawal gp.

Clinical Chemistry: The following statis. sig. changes occurred: increases in aspartate aminotransferase in all gentamicin (GM) and cefotetan (CFT) + G gps. Seen in the withdrawal gps up to day 16 of withdrawal, but not later; also increases in creatinine in all the treated gps "but none of these group mean values during the dosing period exceeded the range of mean values seen pre-study."

Urinalysis: Reduced Na values were seen in Gps IV, V & VI, but not in the withdrawal period. Glucose increases were reported in gps II, III & VI. The former (Na) is a CFT effect, the latter (glucose) is a GM effect. The glucose effect is attributed to the gentamicin destructive of the proximal convoluted tubules.

Organ Weights: (kidneys only) Abs. & rel. kidney wts were increased in Gp III rats & Gp VI M. Withdrawal gp kidneys were normal.

Gross Pathology: Pale kidneys were seen in 4/5 gp III & 2/5 gp VI M and 2/5 Gp III & 1/5 Gp VI F; cecal enlargement was seen in Gps IV, V & VI.

Histopathology: (kidneys only) Gentamicin (GM) toxicity included tubular dilatation, mononuclear cell infiltrate, tubular collapse necrosis/degeneration and other changes. Cefotetan (CFT) when combined with GM appeared to lessen the renal toxicity of GM. CFT toxicity was enlarged ceca. Also histochemically, alkaline phosphatase showed a loss of activity from the brush borders in the GM treated & GM & CFT groups, but less so in the GM & CFT gps. The kidney toxicity appeared to have lessened in Gps V & VI reversible animals.

D. Teratology Study in Rabbits

Procedure: Pregnant rabbits (mating activity & existence of sperm in vagina = day 0 of pregnancy), 11/gp, were IV administered the test formulation (dissolved in saline) from days 6-18 of pregnancy at 0, 50, 200 & 800mpk. The does were killed on day 29 of pregnancy.

Results:

1. Treated dams consumed less food (1/5-1/8 controls) and lost wt.

2. Only 2/11, 3/11 & 4/9 dams bore live fetuses at the LD, MD & HD, respectively. "Controls had 10/10 that accomplished this." Note: the decrease in numbers of treated F were due to accidental breaking of their backs while in the stocks.

3. The lack of sufficient numbers of viable fetuses invalidates this study with respect to determining whether or not the drug formulation is teratogenic to the rabbit.

MUTAGENICITY (Dominant Lethal Study in the Mouse)

Procedure: Male mice (mature) were treated as follows: CFT = cefotetan, EMS - ethylmethanesulfonate (positive control).

Group	Treatment	M	F
1	Control (no treatment)	100	107
2	N. Saline, IV	20	157
3	EMS @ 100mpk, IP	24	168
4	CFT @ 2 gpk, IV	20	183
5	CFT @ 1 gpk, IV	20	153
6	CFT @ 0.5 gpk, IV	20	152

The above were administered as single dose. The treated M were then mated with F (1:1 basis) or 1 different F/week for 7 weeks. The pregnant F were laparotomized on day 13, examined, etc. The non-pregnant mated F were laparotomized on day 21 (after mating).

Results:

1. There were 4 EMS deaths.

2. The following were comparable between control & cefotetan treated gps: mating rate in M, fertility index in F, no. corpora lutea, no. implantations, no. pre-implantation losses, no. F with 2 or more dead fetuses, induced dominant lethality & dominant lethality mutation rate. The rate & no. pre-implantation losses were sig. increased in wk 1 in CFT gps at 1 gpk & with EMS. In CFT a 2 gpk, the no. post-implantation deaths was increased in wk 3. With CFT at 2 gpk, the no. of F with dead fetuses was increased at wk 3. In some of the above positive findings for CFT, when they were subjected to further statis. analysis, they were not sig. different from untreated controls.

It would appear that cefotetan has no dominant lethal effect upon the mouse.

IMMUNOLOGY

"Immunogenicity of an antibiotic, Cefotetan disodium (YM09330), was investigated in mice, guinea pigs and rabbits for its antibody production. Immunological cross reactivity to other antibiotics was also tested using anti Cefotetan rabbit antisera by heterologous passive cutaneous anaphylaxis in guinea pigs and also by passive hemagglutination test. Possible influence on human red blood cells was also investigated by direct Coombs test.

The results indicated no immunogenicity of Cefotetan in animals when immunized with the drug alone with adjuvants. Rabbit antibody produced by immunization of Cefotetan-RSA conjugate showed extremely high specificity to Cefotetan. No direct diverse effect of Cefotetan on human red blood cells was evidenced by direct Coombs test."

PHARMACOKINETICS STUDIES I (Japan)

When cefotetan was orally administered to dogs (50mpk) and the rat (100mpk), the results of plasma conc'ns & urinary excretion in the dog & biliary excretion in the rat showed that there was very little CFT absorption from the GI tract.

When CFT is IV administered to various species of animals at 20mpk results showed that it is excreted mainly in the bile & urine. Almost half of the administered drug is excreted in the bile in the rat, whereas the urinary excretion is higher than the biliary excretion in the mouse, rabbit, dog & monkey.

When CFT was IM injected into the rat & dog and SC into the mouse, the results of urinary, biliary & fecal excretions were comparative to those following IV administration.

The tissue conc'n after IV admin. (20mpk) varied between species as follows:

Rats: kidneys > plasma > liver > lungs > heart > spleen

Dogs: kidneys > liver > plasma > lungs > spleen > heart

Monkeys: kidneys > plasma > lungs > liver > heart > spleen

Mice: kidneys > liver > plasma > lungs > heart > spleen

Rabbits with staphylococcal meningitis that were injected with cefotetan at 100mpk showed a conc'n of the drug in the spinal fluid that was about 1% that of the maximum serum conc'n of the drug.

Labelled cefotetan was administered IM to rats at 20mpk 2x/day for 7.5 days. The conc'n of CFT in the blood, plasma & various organs were comparable at 30 min. & 24 hrs after the 15th treatment, as when measured at the same periods of time after the initial treatment - with one exception. The kidneys were increased over 3-fold at 30 min. and over 6-fold at 24 hrs after the 15th treatment, as compared to these same periods of time after the initial treatment. "The half-life for ^{14}C-CTT (cefotetan) in plasma and most tissues was in the region of one day, whereas for skin it was 8 days and for the kidney, 1-2 weeks." Also, almost 97% of the administered drug was excreted in the urine & feces within 24 hrs after the last treatment.

Cefotetan was IV administered to dogs at 25mpk 2x/day for 21 days or IV administered at 20mpk (total dose) at 4 different times at 3-hr intervals. In neither study was any evidence of cefotetan accumulation seen.

Cefotetan & Its Tautomer:

"Following intravenous injection of ^{14}C-CTT at 20mg/kg, TLC-radiochromatoscanning was conducted. No peaks due to substances other than CTT and its tautomer appeared in the urine, bile or feces of rats nor in the urine or bile of monkeys."

Cefotetan is in chemical equilibrium with its tautomer in solution. At a pH of 7 or less, no tautomer is found; however, its conc'ns are increased with an increase in pH & magnesium conc'ns.

The following tables are self-explanatory:

Area under blood concentration curve of the tautomer in animals receiving CTT at 20 mg/kg i.v.

		Rats	Rabbits	Dogs	Monkeys
Area under blood concentration curve (mcg.hr/ml)	Tautomer	0.7	0.8	1.4	3.3
	CTT + Tautomer	25.4	47.3	76.9	225.4
Tautomer concentrations relative to total concentrations of drug (%)		2.7	1.7	1.7	1.5

Table 13 : Faecal concentrations of the tautomer in animals receiving CTT at 20 mg/kg i.v. (per cent recovery in 0 to 72 hours)

	Animal Species			
	Rats (n=6)	Rabbits (n=3)	Dogs (n=5)	Monkeys (n=3)
CTT + Tautomer	35.5	1.19	17.4	4.47
Tautomer	5.85	0.26	3.28	0.35

The tautomer of CFT was IV administered to the rat, rabbit, dog & monkey at 20mpk. At 30 minutes (based on Area Under Plasma Con'cn Curve figures) the tautomer, relative to the total conc'n (tautomer + CFT) was 81, 79, 65 & 73% in the rat, rabbit, dog & monkey, respectively. At 1 hr in the dog and 2 hrs in the rabbit & monkey, CFT exceeded the level of its tautomer. Also in the rat dosed with the tautomer, CFT & its tautomer were found in the lungs, liver & kidneys - comparable to that found in the plasma.

In summary: "A small amount of YM09330 was converted to its tautomer in the urine of mice, rats and dogs, but a large amount of the tautomer was detected in the urine of rabbits and monkeys." The tautomer has a 3-hydroxy-4-carboxy isothiazole ring at the 7-B-position of the B-lactam skeleton. Also, according to the investigators, the antibacterial activities of the tautomer were the same as cefotetan. Other than the tautomer and cefotetan, there was no metabolite seen in the blood, urine, etc.

PHARMACOKINETICS II (UK)
The following table summarized well the data obtained by ICI, UK.

Dosing routes	Intravenous	Intraperitoneal		Intramuscular		Oral
Study numbers	156,834 PART 01	156,834 PART 01		156,834 PART 02	TAB 912	156,834 PART 01
Sex	Male	Male	Female	Male	Male + Female	Male
Dose and frequency	Single 100 mg/kg	Single 100 mg/kg		Single 200 mg/kg	Daily (28 days) 100, 200 ,250 mg/kg*	Single 100 mg/kg
Plasma elimination half-life (minutes)	19	24	25	27	24	ND
AUC ($\mu g.ml^{-1}.hr$)	144	165	120	156	NC	< 4 **
Mean cefotetan recovery in urine ± Se (n=3) (% of dose)	36.9 ± 3.0	37.8 ± 4.5	28.3 ± 10.2	39.6 ± 1.5	NM	< 5%

NC - Not calculated because of insufficient data.
NM - Not measured because urine not collected
ND - No data.
* - Supplemented by intraperitoneal doses for rats over 200 g body weight
** - AUC (0 2h)

Table 15 - Cefotetan pharmacokinetic data after single and multiple doses to rats.

SUMMARY

Stuart Pharmaceuticals has submitted APACEF^R (cefotetan disodium for injection; ICI 156,834; YM9330) a new cefamycin antibiotic for parenteral administration. The cefamycins are similar to the cephalosporins, but they are derived from Streptomyces species, and they differ structurally in having a methoxy group substituted at the 7 position (lactam ring) on the cephem nucleus. A recently approved member of this class is cefoxitin (Mefoxin; MS&D). Cefotetan is a semisynthetic derivative of organomycin G produced by Streptomyces organonesis. It is reported to be very stable against beta-lactamases of gram-negative bacteria. It is especially active against Escherichia coli, Hemophilus influenzae, Klebsiella spp., Proteus mirabilis and indole-positive Proteus.

This antibiotic was developed by the Yamanouchi Pharmaceutical Co., Tokyo, Japan, who also performed most of the animal studies.

The usual adult dose (not administered to children) is 1 or 2 gm (80mpk/50kg person) administered IV or IM every 12 hrs for 5-10 days. For life-threatening situations, a daily dose of 6 gm (3 gm q 12 h or 120mpk/50kg adult) can be administered.

Additional animal studies are as follows:

Acute IV studies showed that degraded preparations and minor components of CFT were no more toxic to the rat the CFT itself. The solid degraded product was obtained by storing solid CFT for 2 mos. at 50°C; the degraded sol'n was obtained by storing a sol'n of CFT in normal saline for 3 days at 25°C. The minor components are less than 1% CFT. The degradation products and the tautomer of CFT also demonstrated no pharmacologic activity. The tautomer was found in plasma at about 1-2%; it is increased by high pH and magnesium conc'ns, as found in rabbit & monkey urines.

A 3-month IM, IP study in the rat at 100-250mpk/day resulted in reduced Hb, RBC & PCV values at the HD and a decreased Na excretion in all treated gps. Na excretion was normal in a reversible gp. The only drug-related pathology reported was enlarged ceca, which is a common finding with antibiotic treatment. The investigators considered 200mpk to be the "no-effect" dose; apparently, the effect upon Na excretion was not considered to be a drug effect. A 5-week IP study of MMT (minor component of CFT) given at much higher levels than would normally be given, showed no unusual toxicity other than decreases in triglycerides and alkaline phosphatase.

Subnephroscapular hemorrhage that was found to occur with CFT admin. was also found to occur with other closely-related antibiotics.

A 28-day IV study in the rat in which CFT & gentamicin (Gm) were administered as a combination and singly, indicated that CFT, when combined with GM, appeared to lessen the renal toxicity of the latter.

A teratology study in the rabbit at IV dose levels of 50-100mpk resulted in such a small no. of viable fetuses in the CFT-treated groups that teratogenicity could not be determined.

CFT was not mutagenic in a dominant lethal st[redacted]he mouse.

Pharmacokinetic studies demonstrated that the test product when administered orally is poorly absorbed in the rat and dog, that when it is IV administered to various species, it is excreted primarily in the urine & bile but varies in this respect in the different species and that in the rat IM & SC administration is comparable to IV administration. In the rat, CFT has a half-life in plasma and most tissues of 1 day, but 8 days in the skin and 1-2 wks in the kidney. In another study in the dog, there was no evidence of CFT accumulation.

RECOMMENDATIONS

Dr. G.C. Debbas has pointed out in his pharm. rev. of [redacted] that, on the basis of some of the animal data and the proposed clinical dosage recommendations, this drug may appear to have a low margin of safety. The target organs are the hematopoietic system (especially anemia), kidney, liver & spleen. However, because histopathology of the target organs was almost always normal, and because many of the adverse findings are reversible and the nephrotoxicity of this formulation is no greater than others of this class, I have no objection to the approval of this application.

Harold Carlin

cc: Orig. NDA
HFN-815 ltr 1/4/85
HFN-815/MO
CSO
HFN-220
HFN-815/HCarlin/smc/12/10/84
R/d init.by:JMDavitt
2120b

NDA

50-588

Supplements

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-580 (Supplement, dated 3/21/85)

Applicant: Stuart Pharmaceuticals (Div. of ICI Americas), Wilmington, DE

Drug: APACEF® (ICI 156,834; Cefotetan Disodium) for Injection

Category: Antibiotic ("cephamycin")

Dosage Form: Lyophilized Injectable for IM or IV administration

Introduction: This supplement is submitted in response to FDA's letter of 12/20/84, which concerned the testicular toxicity that has been found in infant rats treated with cephalosporins having the N-methyl tetrazolyl thiomethyl (NMTT) side chain.

In previously reported acute toxicity studies of cefotetan in 1, 3 & 5-day-old mice and in 2-day-old rats, high IP or IV doses (3.5-5.4 g/kg), apparent effects on testes (e.g., congestion, hemorrhage, atrophic degeneration and size slightly reduced) in both species. Similar effects were also reported in another juvenile rat study (Progress Report of [redacted]
The applicant has also answered our request for a warning statement concerning this effect, and the following additional study has been submitted:

Testicular Toxicity Study in the Neonatal Rat: (Performed by ICI in England)
Procedure: Cefotetan and several other cephalosporin-type antibiotics were tested at the following dosage levels:

	mpk
Control Saline	0
Cefotetan	120, 500, 1000
Cefoperazone	120, 500, 1000
Cefamandole	1000
Moxalactam	1000

Ten pregnant dams were allotted to each gp, 2 M pups were selected from each litter, 1 for dosing, the other as a littermate control or 10 dosed, 10 undosed/gp (9 gps). The animals were administered the respective drugs SC at the doses listed above on days 6 thru 35 (Day 1 = day of littering), then killed. Testes were examined histologically.

Results:

1. Absolute group mean testicular wts were lower than controls (stat. sig.) in all treated gps except in the LD cefotetan; relative testicular weights were reduced in all treated gps.

2. Histopathology: The changes in the treated gps occurred primarily in the seminiferous tubules...."were primarily degenerative in nature. Cells of the spermatogenic series were affected and they included spermatogonia and spermatocytes." Necrosis & giant cells were occasionally seen in the

[redacted]

seminiferous tubules with a loss of spermatogonia & spermatocytes. In one animal (LD) cefotetan showed changes of a "mild nature", manifested by a reduction in sperm maturation. Leydig & Sertoli cells (testes) and epididymis were not affected. The following tabulation is presented:

LESIONS	GROUP	I	II	III	IV	V	VI	VII	VIII	IX
		0 mg/kg (1560834)	120 mg/kg (1560834)	500 mg/kg (1560834)	1000 mg/kg (1560834)	120 mg/kg (C'ZONE)	500 mg/kg (C'ZONE)	1000 mg/kg (C'ZONE)	1000 mg/kg (C'DOLE)	1000 mg/kg (M'TAM)
TESTES:		(10)	(10)	(10)	(10)	(9)	(9)	(10)	(10)	(10)
Seminiferous tubular degeneration										
minimal				2		2				
mild			1	5	1	7	3		1	9
moderate				3	9		6	10	9	9
Focal capsular hemorrhage		1	1							

Summary:

1. This amendment has been submitted in response to our 12/20/84 letter regarding testicular toxicity of certain cephalosporins in young rats.

2. Cefotetan & cefoperazone (positive control drug) were administered SC to 6-day-old rats for 30 consecutive days at 120, 500 & 1000 mpk/day. Cefamandole and moxalactam were also tested, but only at a high dose (1000 mg/kg). Loss in testicular wt and seminiferous degeneration occurred in all treated gps. At the lower dose levels, cefoperazone appeared to be somewhat more testiculotoxic than cefotetan. At 1000 mpk, however, all the tested antibiotics produced comparable testicular toxicity.

3. The applicant has proposed the following statement for inclusion in the package insert:

"Although the effect in man is not known, mild seminiferous tubular degeneration manifested by a reduction in sperm maturation was noted in 1 of a group of 10 neonatal rats following 30 days of subcutaneous treatment with cefotetan disodium at 120 mg/kg. This dosage represents approximately 2 to 4 times the usual adult human dose. Rats 7 weeks of age treated with up to 1,000 mg/kg/day subcutaneously, as well as 3 week old Beagle dogs treated intravenously with up to 300 mg/kg/day for 5 weeks, did not demonstrate this effect."

Recommendations:

1. Although the labelling of applicant's product includes no pediatric claims, I would urge that further study be done in the rat to determine (a) if the lesions are reversible and (b) if male reproductive capability is adversely affected (e.g., a breeding study). However, it may not be equitable to make this mandatory, since there are other similarly acting cephalosporins marketed (some having pediatric claims), i.e., this applicant perhaps should not be singled out.

2. The beagle dog & rat studies referred to in the proposed labeling were performed by Yamanouchi Pharm. Co. in Japan. There was no testicular atrophy detected in these studies, and apparently no histological evidence of an adverse testicular effect. The dog findings may be of interest, but the rats were beyond the age known to be sensitive to the NMTT effect. [redacted])

3. The proposed labeling changes should be reviewed in the context of the policy being developed for all these structurally-related cephalosporins (I believe Dr. Debbas is coordinating this).

4. A meeting with the applicant is scheduled for May 20.

Harold Carlin

Harold Carlin

cc: Orig. NDA
HFN-815 & 7 cl.ltrs
HFN-815/MO
CSO
Debbas
HFN-340
HFN-815/HCarlin/smc/5/17/85
R/d init.by:JMDavitt
3825b

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-588 (Supplement, dated 3/21/85)

Applicant: Stuart Pharmaceuticals (Div. of ICI Americas), Wilmington, DE

Drug: APACEF^{R} (ICI 156,834; Cefotetan Disodium) for Injection

Category: Antibiotic ("cephamycin")

Dosage Form: Lyophilized Injectable for IM or IV administration

Introduction: This supplement is submitted in response to FDA's letter of 12/20/84, which concerned the testicular toxicity that has been found in infant rats treated with cephalosporins having the N-methyl tetrazolyl thiomethyl (NMTT) side chain.

In previously reported acute toxicity studies of cefotetan in 1, 3 & 5-day-old mice and in 2-day-old rats, high IP or IV doses (3.5-5.4 g/kg), apparent effects on testes (e.g., congestion, hemorrhage, atrophic degeneration and size slightly reduced) in both species. Similar effects were also reported in another juvenile rat study (Progress Report of [redacted]
The applicant has also answered our request for a warning statement concerning this effect, and the following additional study has been submitted:

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Moxalactam	1000

Ten pregnant dams were allotted to each gp, 2 M pups were selected from each litter, 1 for dosing, the other as a littermate control or 10 dosed, 10 undosed/gp (9 gps). The animals were administered the respective drugs SC at the doses listed above on days 6 thru 35 (Day 1 = day of littering), then killed. Testes were examined histologically.

Results:

1. Absolute group mean testicular wts were lower than controls (stat. sig.) in all treated gps except in the LD cefotetan; relative testicular weights were reduced in all treated gps.

2. Histopathology: The changes in the treated gps occurred primarily in the seminiferous tubules...."were primarily degenerative in nature. Cells of the spermatogenic series were affected and they included spermatogonia and spermatocytes." Necrosis & giant cells were occasionally seen in the

seminiferous tubules with a loss of spermatogonia & spermatocytes. In one animal (LD) cefotetan showed changes of a "mild nature", manifested by a reduction in sperm maturation. Leydig & Sertoli cells (testes) and epididymes were not affected. The following tabulation is presented:

LESIONS	GROUP	I	II	III	IV	V	VI	VII	VIII	IX
		0 mg/kg 1356834	120 mg/kg 1356834	500 mg/kg 1356834	1000 mg/kg 1356834	120 mg/kg C'ZONE	500 mg/kg C'ZONE	1000 mg/kg C'ZONE	1000 mg/kg C'DOLE	1000 mg/kg M'TAM
TESTES:										
Seminiferous tubular degeneration		(10)	(10)	(10)	(10)	(9)	(9)	(10)	(10)	(10)
minimal				2		2				
mild			1	8	1	7	3		1	5
moderate				2	9		6	10	9	5
Focal capsular hemorrhage		1	1							

Summary:

1. This amendment has been submitted in response to our 12/20/84 letter regarding testicular toxicity of certain cephalosporins in young rats.

2. Cefotetan & cefoperazone (positive control drug) were administered SC to 6-day-old rats for 30 consecutive days at 120, 500 & 1000 mpk/day. Cefamandole and moxalactam were also tested, but only at a high dose (1000 mg/kg). Loss in testicular wt and seminiferous degeneration occurred in all treated gps. At the lower dose levels, cefoperazone appeared to be somewhat more testiculotoxic than cefotetan. At 1000 mpk, however, all the tested antibiotics produced comparable testicular toxicity.

3. The applicant has proposed the following statement for inclusion in the package insert:

"Although the effect in man is not known, mild seminiferous tubular degeneration manifested by a reduction in sperm maturation was noted in 1 of a group of 10 neonatal rats following 30 days of subcutaneous treatment with cefotetan disodium at 120 mg/kg. This dosage represents approximately 2 to 4 times the usual adult human dose. Rats 7 weeks of age treated with up to 1,000 mg/kg/day subcutaneously, as well as 3 week old Beagle dogs treated intravenously with up to 300 mg/kg/day for 6 weeks, did not demonstrate this effect."

Recommendations:

1. Although the labelling of applicant's product includes no pediatric claims, I would urge that further study be done in the rat to determine (a) if the lesions are reversible and (b) if male reproductive capability is adversely affected (e.g., a breeding study). However, it may not be equitable to make this mandatory, since there are other similarly acting cephalosporins marketed (some having pediatric claims), i.e., this applicant perhaps should not be singled out.

2. The beagle dog & rat studies referred to in the proposed labeling were performed by Yamanouchi Pharm. Co. in Japan. There was no testicular atrophy detected in these studies, and apparently no histological evidence of an adverse testicular effect. The dog findings may be of interest, but the rats were beyond the age known to be sensitive to the NMTT effect. [redacted]

3. The proposed labeling changes should be reviewed in the context of the policy being developed for all these structurally-related cephalosporins (I believe Dr. Debbas is coordinating this).

4. A meeting with the applicant is scheduled for May 20.

Harold Carlin
Harold Carlin

cc: Orig. NDA
HFN-815 ET 6/11/85
HFN-815/MO
CSO
Debbas
HFN-340
HFN-815/HCarlin/smc/5/17/85
R/d Init.by:JMDavitt
3825b

Signed 1/4/85

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-588 (Original Submission, dated 1/31/84)

Date Review Completed: 3/2/84

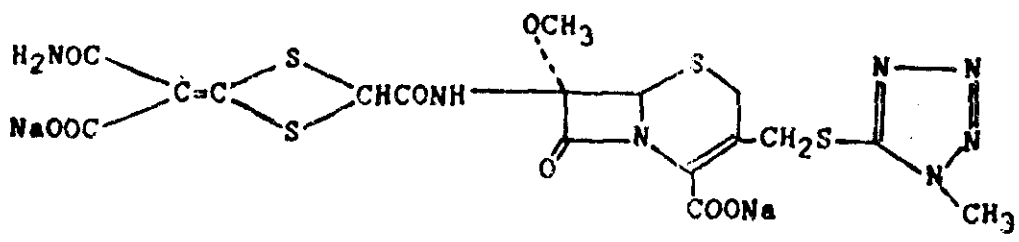
Applicant: Stuart Pharmaceuticals (Div. of ICI Americas), Wilmington, Del.

Drug: APACEF™ (cefotetan disodium) for injection

Code Name: ICI 156,384 (Japan); YM09330 (UK)

Category: Antibiotic ("cephamycin")

Chemical Structure:



Dosage Form: Lyophilized Injectable for IM or IV admin.

Related Submission: [redacted]

Drug Source: Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan

Dosage & Admin.: The usual adult dosage (it is not administered to children) is 1 or 2gm (80mpk/50kg adult) administered IV or IM, q 12 h for 5-10 days. For life-threatening situations, a daily dose of 6gm (3g q 12 h, or 120mpk/50kg adult) can be administered. This is the maximum daily dose and should not be exceeded.

APACEF™ is supplied as a powder in vials containing cefotetan disodium equivalent to 500mg, 1gm & 2gm cefotetan activity for IV & IM administration.

The following animal studies are new and have not been previously reviewed. Unless otherwise designated, these experiments were performed by the Yamanouchi Pharmaceutical Co., Ltd.

[redacted]

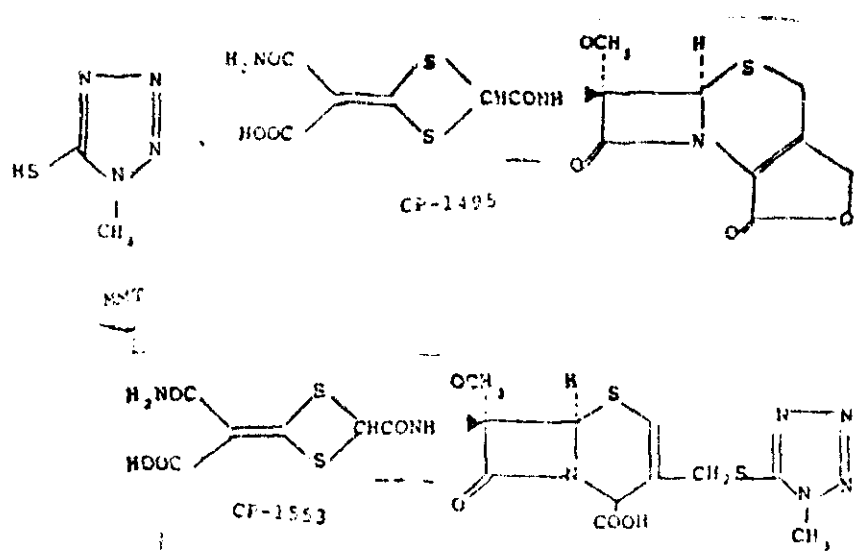
ACUTE TOXICITY

A. Acute Intravenous Study in the Rat

Compound	Sex	LD_{50} (mg/kg)	95% Conf. Limit
Degraded preparation	M	6.58	(6.16-7.03)
	F	5.58	(5.23-5.97)
Degraded 25% sol'n	M	7.35	(6.88-7.85)
	F	6.18	(5.73-6.66)
Tetrazol (MMT)	M	2.37	(2.21-2.54)
	F	2.34	(2.19-2.49)
CP-1495	M	>1.00	
	F	>1.00	
CP-1553	M	>1.00	
	F	>2.00	

Observations: "Toxic signs observed after administration of two kinds of degradation products were the same as those observed in mice given YM09330.

Similar toxic symptoms were seen, but to a lesser extent, in animals which received tetrazol." Almost all animals receiving CP-1495 & C-1553 exhibited decreased locomotor activity and mild bradypnea.



Note: MMT, CP-1495 & CP-1553 are minor components of cefotetan disodium and are less than 1% of the drug.

B. Acute Subnephrocapsular Study

In a previous acute study in mice subnephrocapsular hemorrhage occurred with cefotetan admin. The purpose of this experiment was to determine if this effect was found in similar compounds, or peculiar to cefotetan only. The following 7 were tested: cefmetazole (CMZ), cefazolin (CEZ), cephalothin (CET), cefoperazone (T-1551), latamoxef (6059-S), carbenicillin (CBPC) & sulbenicillin (SBPC). The Na salts were used in all cases.

Procedure: F mice, 10/group, were IV administered 5g/kg (T-1551, 4g/kg) or saline (N, 6%).

Results: Subnephrocapsular hemorrhage occurred with the following preparations: cefotetan, 60595, CBPC & SBPC.

The investigators concluded that subnephrocapsular hemorrhage is not specific to only cefotetan disodium, but also to B-lactam antibiotics (disodium salts) which dissociate to divalent radicals.

SUBACUTE TOXICITY

A. 5-Week Intraperitoneal Study of MMT in the Rat

Procedure: Male rats (SD CRJ-CD strain) Charles River, Japan, were divided into 3 groups (12/gp) and IP administered MMT (a minor component of CFT) at 0, 5 & 100mpk, which corresponds to 500-1000mpk of cefotetan disodium (LD) and "a 20x higher dosage" of the HD. Half the animals were treated for 3 wks, the other half for 5 wks. The animals were killed at the above time periods and necropsies performed.

Results:

1. There were no deaths or abnormal clinical signs.

2. Body wt gain was reduced in HD beginning day 10.

3. Hematology was normal (PCV only was tested).

4. Three week rats showed decreases in triglycerides and phospholipids (HD). Five week rats showed decreases in triglycerides & alkaline phosphatase (HD).

5. Rel. & abs. liver & kidney wts were comparable to controls.

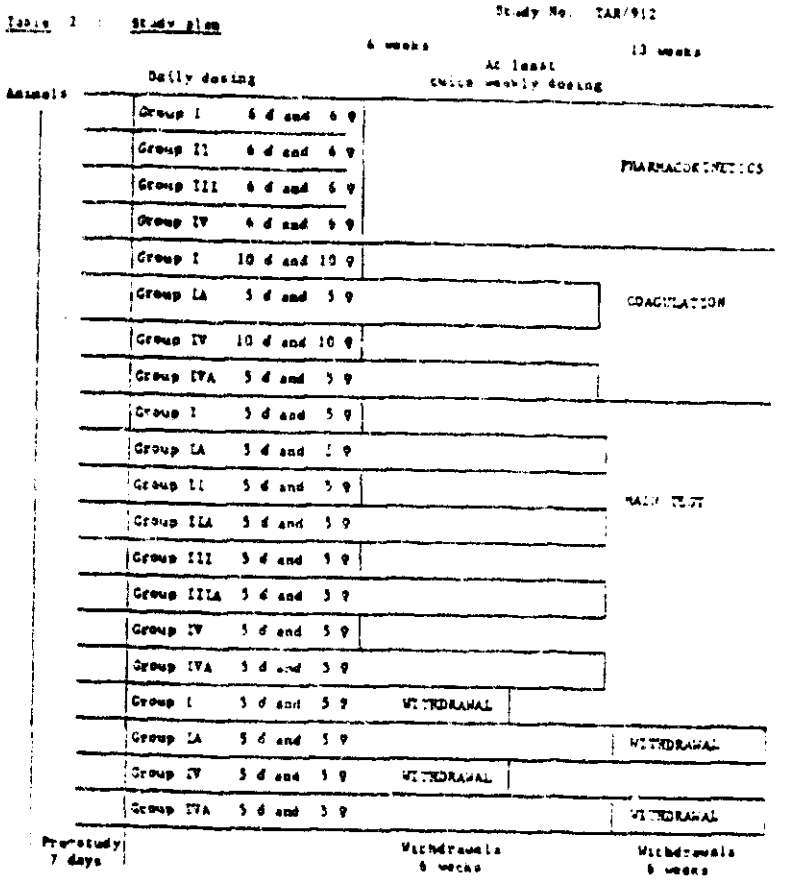
6. Histopathology: ...rosis occurred in the parietal peritoneum and the visceral peritoneum of the liver and its surrounding organs." The parenchymal areas of these organs were not affected. These changes are ascribed to the local irritation of the drug.

B. Three-month Intramuscular Study in Rat (ICI-[illegible])

The design of this experiment can be somewhat confusing and is easiest to understand by including the following tables taken from the submission.

Table 1 : Study plan

Study No. TAR/912



DOSES

Group I (Control):	0	mg/kg/day :	26 d and 26 ♀	)	
IA	0	mg/kg/day :	15 d and 15 ♀	)	
II	100	mg/kg/day :	11 d and 11 ♀	)	- DOSING FOR 1 MONTH
IIA	100	mg/kg/day :	5 d and 5 ♀	)	
III	200	mg/kg/day :	11 d and 11 ♀	)	NB Groups IA, IIA, IIIA
IIIA	200	mg/kg/day :	5 d and 5 ♀	)	and IVA dosed at least
IV	400	mg/kg/day :	26 d and 26 ♀	)	twice weekly only, for
IVA	450	mg/kg/day :	15 d and 15 ♀	)	1 month interim kill
			116 d and 116 ♀	)	

The unique ICI animal identification numbers to be used in this study are shown in Appendix V.

Additional Information:

1. The active material was dissolved in 0.5% aq. lignocaine.

2. "All rats were injected daily into the musculature...up to a limit of 0.2ml/animal. When this limiting volume of injection was reached for each animal (200g body wt) the remainder of the dose was given intraperitoneally..."

3. The Gps I, II, III & IV animals were killed after 28-32 days of dosing. The Gps IA, IIA, IIIA or IVA were injected for 13 wks (84-88 days).

4. Additionally, 5/sex rats in each of Gps I, IV, IA & IVA were dosed at the same time as the main test gps for 1 mo. & 3 mos. with each treatment period followed by a 6-wk withdrawal period before necropsy.

Mortality: None

Food Consumption: Normal

Body Wt Gain: Decreased in M of Gp III & IV beginning about the 7th & 8th wks, respectively

Ophthalmological Exam: Normal

Blood Pressure, Heart Rate, Body Temp: Normal

Hematology: At 12 wks, gp IVA showed reduced Hb, RBC & PCV values.

Clinical Chemistry: No sig. findings

Urinalysis: Decreased Na values were seen in the 3-mo. treated gps at 4 & 12 wks; also in the 1-month animals at days 9 & 23. This was not seen in the reversible gp.

Organ Weights: Relative liver wts were reduced in all 1 & 3-month treated gps, except Gp IVA F. The reversible groups were normal except for Gp IV F, which showed a reduced rel. liver wt. Liver (abs.) wts were also reduced in many of the 1 & 3-month treated gps.

Gross Pathology: (I, IA, IV & IVA main & withdrawal gps): All the treated animals, with 1 exception (1 Gp 3 F) showed distended ceca - a common finding with antibiotic treatment. The control and withdrawal gps did not show extended ceca.

Histopathology: Related to the local effects of the drug and/or its vehicle at the injection sites were hemorrhage, siderosis & chronic inflammatory cell infiltration. Also, an "increased incidence of bruising in GP IV & IVA may be related to the increased viscosity of the dosing solution at higher dose levels."

Pharmacokinetic Studies: The following was obtained from the gps from which blood was obtained at 28 days.

1. Plasma conc'ns were linear to dose levels.

2. Half-life of the test formulation was 24 min. (0.25-2 hrs).

3. Highest conc'ns were detected at 15 min. post-dose.

C. 28-Day Cefotetan-Gentamicin Intravenous Study in Rats (ICI-UK)

Study Design:

	No. of Animals		
	1 Month	+ 6-wk w'draval	Dose Levels (mpk)
Group: I	5/sex	5/sex	0 (saline)
II	"	0	20 (gentamicin)
III	"	0	40 (gentamicin)
IV	"	0	100 (cefotetan)
V	"	5/sex	100 + 20 (cefot. + gent.)
VI	"	5/sex	100 + 40 (" " ")

Note: Circumstances may arise where gentamicin, a nephrotoxic drug, may be used in conjunction with cefotetan. Is this nephrotoxicity enhanced when the two are administered together?

Route & Duration: Cefotetan was IV administered up to day 10. "As a result of difficulties experienced in multiple dosing, the route of administration was changed to intraperitoneal for the remainder of the study - 28 days." (Difficulties experienced were cyanosis of tails & difficulty in injecting into the tail vein.) "Previous pharmacokinetic studies....indicated very little difference in bioavailability with either route."

Mortality: None

Food Intake; Body Wt Gain; Ophthalmological Exam: Normal

Water Intake: Increased in treated gps; normal in withdrawal gp.

Clinical Chemistry: The following statis. sig. changes occurred: increases in aspartate aminotransferase in all gentamicin (GM) and cefotetan (CFT) + G gps. Seen in the withdrawal gps up to day 16 of withdrawal, but not later; also increases in creatinine in all the treated gps "but none of these group mean values during the dosing period exceeded the range of mean values seen pre-study."

Urinalysis: Reduced Na values were seen in Gps IV, V & VI, but not in the withdrawal period. Glucose increases were reported in gps II, III & VI. The former (Na) is a CFT effect, the latter (glucose) is a GM effect. The glucose effect is attributed to the gentamicin destructive of the proximal convoluted tubules.

Organ Weights: (kidneys only) Abs. & rel. kidney wts were increased in Gp III rats & Gp VI M. Withdrawal gp kidneys were normal.

Gross Pathology: Pale kidneys were seen in 4/5 gp III & 2/5 gp VI M and 2/5 Gp III & 1/5 Gp VI F; cecal enlargement was seen in Gps IV, V & VI.

Histopathology: (kidneys only) Gentamicin (GM) toxicity included tubular dilatation, mononuclear cell infiltrate, tubular collapse necrosis/degeneration and other changes. Cefotetan (CFT) when combined with GM appeared to lessen the renal toxicity of GM. CFT toxicity was enlarged ceca. Also histochemically, alkaline phosphatase showed a loss of activity from the brush borders in the GM treated & GM & CFT groups, but less so in the GM & CFT gps. The kidney toxicity appeared to have lessened in Gps V & VI reversible animals.

D. Teratology Study in Rabbits

Procedure: Pregnant rabbits (mating activity & existence of sperm in vagina = day 0 of pregnancy), 11/gp, were IV administered the test formulation (dissolved in saline) from days 6-18 of pregnancy at 0, 50, 200 & 800mpk. The does were killed on day 29 of pregnancy.

Results:

1. Treated dams consumed less food (1/5-1/8 controls) and lost wt.

2. Only 2/11, 3/11 & 4/9 dams bore live fetuses at the LD, MD & HD, respectively. "Controls had 10/10 that accomplished this." Note: the decrease in numbers of treated F were due to accidental breaking of their backs while in the stocks.

3. The lack of sufficient numbers of viable fetuses invalidates this study with respect to determining whether or not the drug formulation is teratogenic to the rabbit.

MUTAGENICITY (Dominant Lethal Study in the Mouse)

Procedure: Male mice (mature) were treated as follows: CFT = cefotetan, EMS - ethylmethanesulfonate (positive control).

Group	Treatment	M	F
1	Control (no treatment)	100	107
2	N. Saline, IV	20	157
3	EMS @ 100mpk, IP	24	168
4	CFT @ 2 gpk, IV	20	183
5	CFT @ 1 gpk, IV	20	153
6	CFT @ 0.5 gpk, IV	20	152

The above were administered as single dose. The treated M were then mated with F (1:1 basis) or 1 different F/week for 7 weeks. The pregnant F were laparotomized on day 13, examined, etc. The non-pregnant mated F were laparotomized on day 21 (after mating).

Results:

1. There were 4 EMS deaths.

2. The following were comparable between control & cefotetan treated gps: mating rate in M, fertility index in F, no. corpora lutea, no. implantations, no. pre-implantation losses, no. F with 2 or more dead fetuses, induced dominant lethality & dominant lethality mutation rate. The rate & no. pre-implantation losses were sig. increased in wk 1 in CFT gps at 1 gpk & with EMS. In CFT a 2 gpk, the no. post-implantation deaths was increased in wk 3. With CFT at 2 gpk, the no. of F with dead fetuses was increased at wk 3. In some of the above positive findings for CFT, when they were subjected to further statis. analysis, they were not sig. different from untreated controls.

It would appear that cefotetan has no dominant lethal effect upon the mouse.

IMMUNOLOGY

"Immunogenicity of an antibiotic, Cefotetan disodium (YM09330), was investigated in mice, guinea pigs and rabbits for its antibody production. Immunological cross reactivity to other antibiotics was also tested using anti Cefotetan rabbit antisera by heterologous passive cutaneous anaphylaxis in guinea pigs and also by passive hemagglutination test. Possible influence on human red blood cells was also investigated by direct Coombs test.

The results indicated no immunogenicity of Cefotetan in animals when immunized with the drug alone with adjuvants. Rabbit antibody produced by immunization of Cefotetan-RSA conjugate showed extremely high specificity to Cefotetan. No direct diverse effect of Cefotetan on human red blood cells was evidenced by direct Coombs test."

PHARMACOKINETICS STUDIES I (Japan)

When cefotetan was orally administered to dogs (50mpk) and the rat (100mpk), the results of plasma conc'ns & urinary excretion in the dog & biliary excretion in the rat showed that there was very little CFT absorption from the GI tract.

When CFT is IV administered to various species of animals at 20mpk results showed that it is excreted mainly in the bile & urine. Almost half of the administered drug is excreted in the bile in the rat, whereas the urinary excretion is higher than the biliary excretion in the mouse, rabbit, dog & monkey.

When CFT was IM injected into the rat & dog and SC into the mouse, the results of urinary, biliary & fecal excretions were comparative to those following IV administration.

The tissue conc'n after IV admin. (20mpk) varied between species as follows:

Rats: kidneys > plasma > liver > lungs > heart > spleen

Dogs: kidneys > liver > plasma > lungs > spleen > heart

Monkeys: kidneys > plasma > lungs > liver > heart > spleen

Mice: kidneys > liver > plasma > lungs > heart > spleen

Rabbits with staphylococcal meningitis that were injected with cefotetan at 100mpk showed a conc'n of the drug in the spinal fluid that was about 1% that of the maximum serum conc'n of the drug.

Labelled cefotetan was administered IM to rats at 20mpk 2x/day for 7.5 days. The conc'n of CFT in the blood, plasma & various organs were comparable at 30 min. & 24 hrs after the 15th treatment, as when measured at the same periods of time after the initial treatm - with one exception. The kidneys were increased over 3-fold at 30 min. and over 6-fold at 24 hrs after the 15th treatment, as compared to these same periods of time after the initial treatment. "The half-life for ^{14}C-CTT (cefotetan) in plasma and most tissues was in the region of one day, whereas for skin it was 8 days and for the kidney, 1-2 weeks." Also, almost 97% of the administered drug was excreted in the urine & feces within 24 hrs after the last treatment.

Cefotetan was IV administered to dogs at 25mpk 2x/day for 21 days or IV administered at 20mpk (total dose) at 4 different times at 3-hr intervals. In neither study was any evidence of cefotetan accumulation seen.

Cefotetan & Its Tautomer:

"Following intravenous injection of ^{14}C-CTT at 20mg/kg, TLC-radiochromatoscanning was conducted. No peaks due to substances other than CTT and its tautomer appeared in the urine, bile or feces of rats nor in the urine or bile of monkeys."

Cefotetan is in chemical equilibrium with its tautomer in solution. At a pH of 7 or less, no tautomer is found; however, its conc'ns are increased with an increase in pH & magnesium conc'ns.

The following tables are self-explanatory:

Table 12 : Area under blood concentration curve of the tautomer in animals receiving CTT at 20 mg/kg i.v.

		Rats	Rabbits	Dogs	Monkeys
Area under blood concentration curve (mcg/ml)	Tautomer	0.7	0.8	1.4	3.3
	CTT + Tautomer	25.4	47.3	76.9	225.4
Tautomer concentrations relative to total concentrations of drug (%)		2.7	1.7	1.7	1.5

Table 13 : Faecal concentrations of the tautomer in animals receiving CTT at 20 mg/kg i.v. (per cent recovery in 0 to 72 hours)

	Animal Species			
	Rats (n=6)	Rabbits (n=3)	Dogs (n=5)	Monkeys (n=3)
CTT + Tautomer	35.5	1.19	17.4	4.47
Tautomer	5.86	0.26	3.28	0.35

The tautomer of CFT was IV administered to the rat, rabbit, dog & monkey at 20mpk. At 30 minutes (based on Area Under Plasma Con'cn Curve figures) the tautomer, relative to the total conc'n (tautomer + CFT) was 81, 79, 65 & 73% in the rat, rabbit, dog & monkey, respectively. At 1 hr in the dog and 2 hrs in the rabbit & monkey, CFT exceeded the level of its tautomer. Also in the rat dosed with the tautomer, CFT & its tautomer were found in the lungs, liver & kidneys - comparable to that found in the plasma.

In summary: "A small amount of YM09330 was converted to its tautomer in the urine of mice, rats and dogs, but a large amount of the tautomer was detected in the urine of rabbits and monkeys." The tautomer has a 3-hydroxy-4-carboxy isothiazole ring at the 7-R-position of the B-lactam skeleton. Also, according to the investigators, the antibacterial activities of the tautomer were the same as cefotetan. Other than the tautomer and cefotetan, there was no metabolite seen in the blood, urine, etc.

PHARMACOKINETICS II (UK)

The following table summarized well the data obtained by ICI, UK.

Dosing routes	Intravenous	Intraperitoneal		Intramuscular		Oral
Study numbers	156,834 PKRT 01	156,834 PKRT 03		156,834 PKRT 02	TAR 912	156,834 PKRT 01
Sex	Male	Male	Female	Male	Male + Female	Male
Dose and frequency	Single 100 mg/kg	Single 100 mg/kg		Single 200 mg/kg	Daily (28 days) 100, 200 ,250 mg/kg*	Single 100 mg/kg
Plasma elimination half-life (minutes)	19	24	25	27	24	ND
AUC ($\mu g.ml^{-1}.hr$)	144	105	120	166	NC	< 4 **
Mean cefotetan recovery in urine ± SE (n=3) (% of dose)	36.9 ± 3.0	37.8 ± 2.5	28.3 ± 10.2	39.6 ± 1.5	NM	< 5%

NC - Not calculated because of insufficient data.
NM - Not measured because urine not collected
ND - No data.
* - Supplemented by intraperitoneal doses for rats over 200 g body weight.
** - AUC (0-2h)

Table 15 : Cefotetan pharmacokinetic data after single and multiple doses to rats.

SUMMARY

Stuart Pharmaceuticals has submitted APACEF^R (cefotetan disodium for injection; ICI 156,834; YM9330) a new cefamycin antibiotic for parenteral administration. The cefamycins are similar to the cephalosporins, but they are derived from Streptomyces species, and they differ structurally in having a methoxy group substituted at the 7 position (lactam ring) on the cephem nucleus. A recently approved member of this class is cefoxitin (Mefoxin; MS&D). Cefotetan is a semisynthetic derivative of organomycin G produced by Streptomyces organonesis. It is reported to be very stable against beta-lactamases of gram-negative bacteria. It is especially active against Escherichia coli, Hemophilus influenzae, Klebsiella spp., Proteus mirabilis and indole-positive Proteus.

This antibiotic was developed by the Yamanouchi Pharmaceutical Co., Tokyo, Japan, who also performed most of the animal studies.

The usual adult dose (not administered to children) is 1 or 2 gm (80mpk/50kg person) administered IV or IM every 12 hrs for 5-10 days. For life-threatening situations, a daily dose of 6 gm (3 gm q 12 h or 120mpk/50kg adult) can be administered.

Additional animal studies are as follows:

Acute IV studies showed that degraded preparations and minor components of CFT were no more toxic to the rat the CFT itself. The solid degraded product was obtained by storing solid CFT for 2 mos. at 60°C; the degraded sol'n was obtained by storing a sol'n of CFT in normal saline for 3 days at 25°C. The minor components are less than 1% CFT. The degradation products and the tautomer of CFT also demonstrated no pharmacologic activity. The tautomer was found in plasma at about 1-2%; it is increased by high pH and magnesium conc'ns, as found in rabbit & monkey urines.

A 3-month IM, IP study in the rat at 100-250mpk/day resulted in reduced Hb, RBC & PCV values at the HD and a decreased Na excretion in all treated gps. Na excretion was normal in a reversible gp. The only drug-related pathology reported was enlarged ceca, which is a common finding with antibiotic treatment. The investigators considered 200mpk to be the "no-effect" dose; apparently, the effect upon Na excretion was not considered to be a drug effect. A 5-week IP study of MMT (minor component of CFT) given at much higher levels than would normally be given, showed no unusual toxicity other than decreases in triglycerides and alkaline phosphatase.

Subnephroscapular hemorrhage that was found to occur with CFT admin. was also found to occur with other closely-related antibiotics.

A 28-day IV study in the rat in which CFT & gentamicin (Gm) were administered as a combination and singly, indicated that CFT, when combined with GM, appeared to lessen the renal toxicity of the latter.

A teratology study in the rabbit at IV dose levels of 50-100mpk resulted in such a small no. of viable fetuses in the CFT-treated groups that teratogenicity could not be determined.

CFT was not mutagenic in a dominant lethal study in the mouse.

Pharmacokinetic studies demonstrated that the test product when administered orally is poorly absorbed in the rat and dog, that when it is IV administered to various species, it is excreted primarily in the urine & bile but varies in this respect in the different species and that in the rat IM & SC administration is comparable to IV administration. In the rat, CFT has a half-life in plasma and most tissues of 1 day, but 8 days in the skin and 1-2 wks in the kidney. In another study in the dog, there was no evidence of CFT accumulation.

RECOMMENDATIONS

Dr. G.C. Debbas has pointed out in his pharm. rev. of [redacted] that, on the basis of some of the animal data and the proposed clinical dosage recommendations, this drug may appear to have a low margin of safety. The target organs are the hematopoietic system (especially anemia), kidney, liver & spleen. However, because histopathology of the target organs was almost always normal, and because many of the adverse findings are reversible and the nephrotoxicity of this formulation is no greater than others of this class, I have no objection to the approval of this application.

Harold Carlin

cc: Orig. NDA
HFN-815 12/4/84
HFN-815/MO
CSO
HFN-220
HFN-815/HCarlin/smc/12/10/84
R/d init.by:JMDavitt
2120b

NUDA
50588

MICRO
REV

DRUG CONTROL REVIEW NOTES

1. TYPE: IND X

2. NO.: 50-588

3. SPONSOR: Stuart Pharmaceuticals, Division of ICI Americas, Inc. Attn: Allan J. Milbauer

4. ADDRESS: Concord Pike & New Murphy Road, Willmington, DE 19897

5. SUBMISSIONS REVIEWED

a. ORIGINAL DATED: Jan. 20, 1984

b. AMENDMENTS DATED: April 6, 1984; April 16, 1984

5c. PROVISIONS FOR:
1. Changes in sample preparation for dosage forms; exhibit samples.
2. Revision of GC for residual solvents.

6. NAME(S)

a. TRADE: Apacef

b. NON-PROPRIETARY: cefotetan disodium for injection

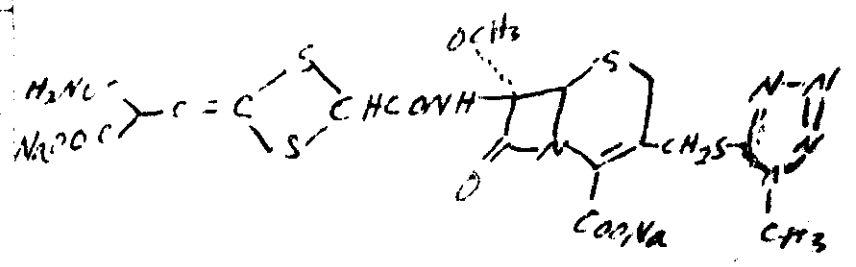
c. CHEMICAL: [6R-(6α,7α)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidine)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, sodium salt.

d. ESTAB: none designated

e. USAN:

f. WHO:

7. STRUCTURAL FORMULA



8. DOSAGE FORM: Injectable
0.5, 1.0, & 2.0 g. vials and
1.0 & 2.0 g. bottles.

9. [X] RX [ ] OTC

10. FAMILY OR TYPE OF DRUG: cephalosporin antibiotic

11. RELATED NDA, IND, MF, FORM 510: [redacted]

12. REMARKS

See attached comments

13. CONCLUSIONS

The manufacturing and controls will be satisfactory when an acceptable CGMP evaluation is received from Compliance, the draft certification monographs are negotiated, and satisfactory draft labeling has been filed. The firm was notified of labeling deficiencies in a telephone conversation dated 5/23/84.

14. DATE REVIEWED: May 23, 1984

15. REVIEWER: James R. King James R. King 5/31/85

FORM FDH-1742

COPY TO: 1. Original IND HFN-815, HFN-815/CSO, HFN-178
2. Duplicate IND HFN-235