NDA: 50-578 TRADE: FORTAZ

SPONSOR: GLAXO INC. GENERIC: CEFTAZIDIME

APPROVAL LETTER: Y STATISTICIAN'S REVIEW: N

SBA: Y BIO/DISSOLUTION REVIEW: Y

FINAL PRINTED LABEL: Y MICROBIOLOGIST'S REVIEW: N

MEDICAL OFFICER'S REVIEW: Y NAS/NRC REVIEW: N

CHEMIST'S REVIEW: N FEDERAL REGISTER NOTICE: N

PHARMACOLOGIST'S REVIEW: Y DATE: 11/19/87

APRVL

LTR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

7/18/85

NDA 50-578

M. David McFarlane, Ph.D.
Glaxo Incorporated
P.O. Box 13960
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McFarlane:

Reference is made to your New Drug Application dated March 20, 1983 submitted pursuant to section 507 of the Federal Food, Drug, and Comsetic Act for the preparation FORTAZ (ceftazidime) for injection.

We also acknowledge receipt of your additional communications dated June 6, 1985 and June 21, 1985.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling.

However, prior to marketing, the following changes must be made in the labeling and twelve copies of the labeling submitted to us:

1. In the heading, there should be more space between the line which reads, "For intravenous or intramuscular use," and the Description section heading.

2. Two commas should be inserted in the first paragraph (lines 8 and 10) of the Clinical Pharmacology section after 69 mcg/ml and 1 g, to read, "...mean peak serum concentrations of 42 mcg/ml, 69 mcg/ml, and 170 mcg/ml, respectively..." and "...following intravenous infusion of 500 mg, 1 g, and 2 g doses..."

3. Change "are" to "is" in the first paragraph of the Microbiology section so that the sentence will begin, "A wide range of gram-negative organisms is susceptible to ceftazidime..."

4. In the seventh paragraph of the Microbiology section, the name Enterobacteriaceae should begin with a captial "E". The name is properly italicized.

5. The last sentence in item #3 of the vial section of the tear-away sheet should read:

> "The withdrawn solution may contain some bubbles of carbon dioxide.
>
> Note: As with the administration of all parenteral products, accumulated gases should be expressed from the syringe immediately before injection of Fortaz."

The labeling should be revised exactly as we have requested above. If additional information relating to the safety or effectiveness of this drug becomes available before the final printed labeling is submitted to FDA, further revision of that labeling may be required.

In addition, please submit in duplicate the advertising copy which you intend to use in your proposed introductory promotional or advertising campaign. Please submit one of the copies directly to the Division of Drug Advertising with a copy of the package insert.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Your cooperation is appreciated.

Sincerely yours,

for James Bukstel

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Form 5 50-578

JUN 3 1985

M. David MacFarlane, Ph.D.
Glaxo Incorporated
P.O. Box 13960
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. MacFarlane:

Reference is made to your Antibiotic Form 5 application dated March 20, 1983 submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for the preparation FORTAZ (ceftazidime) for injection.

We also acknowledge receipt of your additional communications dated August 8 and December 7, 1983; February 2, 7, 15, and 20, March 13 and 26, April 5, 23, and 24, May 3 (two submissions), 22, 23 (two submissions), and 29, June 1, 8, 13, and 21 (two submissions), July 11, 13, 24 (two submissions), and 27 (two submissions), August 2, 7, 13, 17 (two submissions), 24, and 29, September 4, 5, 12, 20, 21 (two submissions), 24, and 28, October 1 (two submissions), 16 (two submissions), 23 (two submissions), 30, November 5, 7, 15, 20, 21, and 28, December 6, 11 (two submissions), 14, 19 (three submissions), 20 (two submissions), 1984; January 3, 8, 9, 10, 16, 22, 29, and 31; and February 4, 5, 7, 15, 18, 25 (two submissions), and 28, 1985.

We have completed the review of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft labeling filed February 5, 1985 except for the following:

1. Item No. 6 in the Indications and Usage section should be revised to read as follows: "6. Gynecological Infections, including endometritis, pelvic cellulitis and other infections of the female genital tract, caused by E. coli."

2. Shelf-life for the frozen state should be revised from 6 months to 3 months everywhere it appears in the insert.

3. The established name for the drug is ceftazidime (not ceftazidime pentahydrate) and it should appear that way in the labeling. Please contact the USAN Council so that the monograph can be modified to indicate that the pentahydrate is being used.

4. The labeling should point out in the "How Supplied" section that the weight of the drug is based on the anhydrous moiety and not on the pentahydrate.

5. Paragraph 6, sentence 1 in the "Microbiology" section of the labeling "as with all cephalosporins..." is ambiguous and should be deleted.

If additional information relating to the safety or effectiveness of this antibiotic becomes available before we receive the final printed labeling, revision of that labeling may be required. Please submit twelve copies of the printed labels and other labeling. Also, please submit patent information for this product as outlined on the enclosed form.

In addition, please update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including those involving indications not being sought in the present submission, other dosage forms or dose levels, etc.

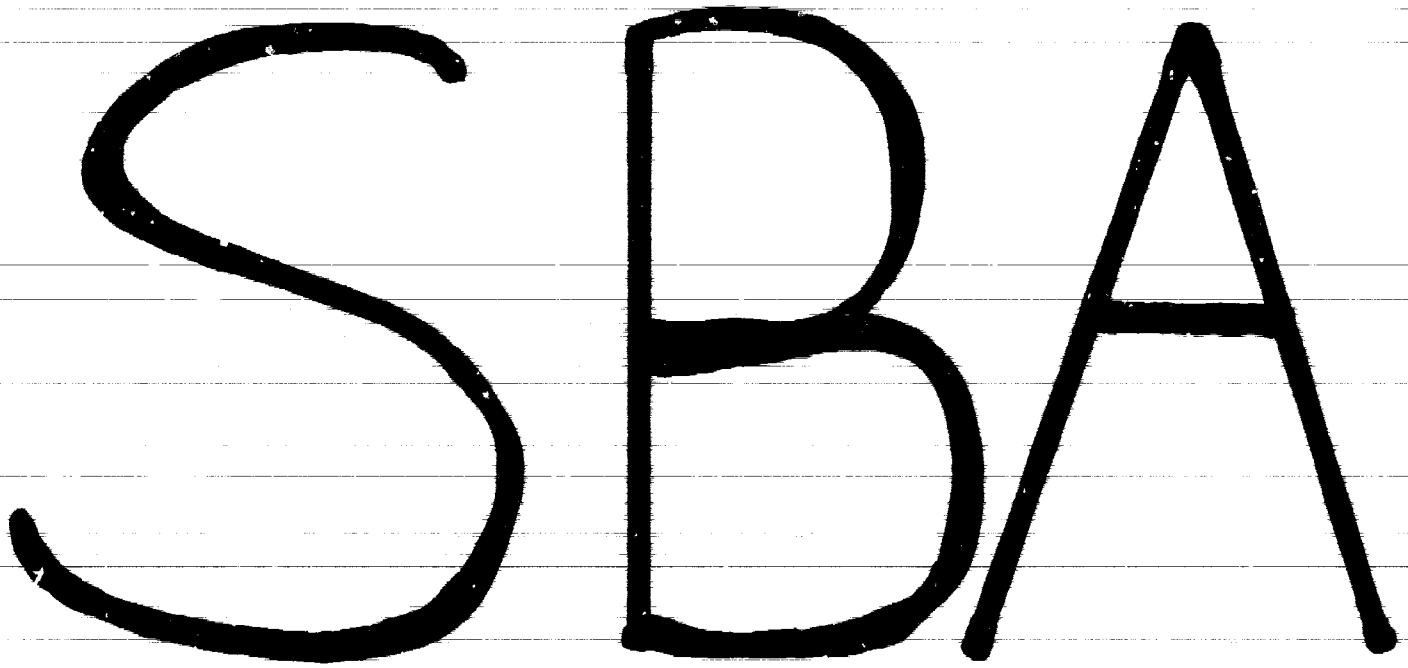
Also, we would appreciate you submitting in duplicate the advertising copy which you intend to use in your proposed promotional or advertising campaign. Please submit one of these copies directly to the Division of Drug Advertising with a copy of the package insert.

The antibiotic may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: ATL-DO
HFN-82
HFN-710
HFN-220
HFN-500/JMinor
HFN-535/RJoyce
HFN-430
HFN-400
HFN-235
HFN-815
HFN-815/CSO/DFowler
HFN-815/MO/Reed/Stanley
HFN-815/MICRO/Norton/King
HFN-815/PHARM/Davitt/Debbas
R/D init. by: ETabor/3/20/85/3/28/85
F/T: 3/26/85/5/15/85/5/28/85
3999b


SBA

SUMMARY BASIS OF APPROVAL

NDA 50-578

Applicant:
Glaxo, Inc.
Research Triangle, NC

Drug Generic Name:
Ceftazidime

Drug Trade Name: FORTAZ™

I. Indications and Usage

FORTAZ™ is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the diseases listed below:

1. Lower Respiratory Tract Infections, including pneumonia due to

- *Pseudomonas aeruginosa*
- *H. influenzae*
- *Klebsiella* species
- *Enterobacter* species
- *P. mirabilis*
- *Pseudomonas* species
- *E. coli*
- *Serratia* species
- *Citrobacter* species
- *S. pneumoniae*
- *S. aureus* (methicillin-susceptible strains)

2. Skin and Skin Structure Infections due to

- *P. aeruginosa*
- *Klebsiella* species
- *E. coli*
- *Enterobacter* species
- *Proteus* species including *P. mirabilis* and indole + *Proteus*
- *Serratia* species
- *S. aureus* (methicillin-susceptible strains)
- *S. pyogenes* (group A beta hemolytic streptococci)

3. Urinary Tract Infections due to

Pseudomonas aeruginosa	Klebsiella species
Enterobacter species	E. coli
Proteus species including P. mirabilis and indole + Proteus	

4. Bacterial Septicemia due to

Pseudomonas aeruginosa	E. coli
Klebsiella species	Serratia species
S. aureus (methicillin-susceptible strains)	H. influenzae
	S. pneumoniae

5. Bone and Joint Infections due to

Pseudomonas aeruginosa	Enterobacter species
Klebsiella species	S. aureus (methicillin-susceptible strains)

6. Gynecological Infections including endometritis, pelvic cellulitis, and other infections of the female genital tract due to E. coli.

7. Intra-abdominal Infections including peritonitis due to

E. coli	S. aureus (methicillin-susceptible strains)
Klebsiella species	

and polymicrobial infections caused by aerobic and anaerobic organisms, including Bacteroides species (many strains of B. fragilis are resistant).

8. Central Nervous System Infections including meningitis due to

H. influenzae	N. meningitidis

Ceftazidime has also been used successfully in a limited number of cases of meningitis due to P. aeruginosa and S. pneumoniae.

Dosage Form, Route of Administration, and Recommended Dosage:

FORTAZ™ is a sterile white or off-white dry-powder blend of two ingredients in vials and infusion bottles to be constituted for intravenous or intramuscular administration.

The usual adult dosage is one gram administered intravenously or intramuscularly every 8 or 12 hours. Generally, FORTAZ should be continued for at least two days after the signs and symptoms of the infection have disappeared, but in complicated infections, longer therapy may be required. The dose and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The following dosage schedule is recommended:

	Dose	Frequency
Adults		
Usual recommended dose	1 g IV or IM	q 8-12 h
Uncomplicated urinary tract	250 mg IV or IM	q 12 h
Bone and joint infections	2 g IV	q 12 h
Complicated urinary tract infections	500 mg IV or IM	q 8-12 h
Uncomplicated pneumonia; mild skin and skin structure infections	500 mg to 1 g IV or IM	q 8 h
Serious gynecological and intra-abdominal infections	2 g IV	q 8 h
Meningitis	2 g IV	q 8 h
Very severe life-threatening infections, especially in immunocompromised patients	2 g IV	q 8 h
Pseudomonal lung infections in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 g/day	q 8 h

	Dose	Frequency
Neonates (0–4 weeks)	30 mg/kg IV	q 12 h
Infants and children (1 month–12 years)	30–50 mg/kg IV to a maximum of 6 g/day+	q 8 h

*Although clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis. +The higher dose should be reserved for immunocompromised children or children with cystic fibrosis or meningitis.

For patients with impaired renal function, it is recommended that the dosage of ceftazidime be reduced as recommended in the labeling to compensate for its slower excretion. No dosage adjustment is necessary for patients with impaired hepatic function.

III. Manufacturing and Controls

Manufacturing and controls, stability, methods validation, labeling, inspections, and environmental-impact evaluation conform to all federal regulations.

IV. Pharmacology

Ceftazidime is a cephalosporin antibiotic for parenteral administration.

On parenteral administration, virtually all of the drug was eliminated intact via the kidneys, though there is some autoradiographic evidence that, in rats, some may be excreted by the gastric mucosa.

In the rat, ceftazidime, in a single subcutaneous dose of 2 g/kg, showed some evidence of nephrotoxicity and it produced tubular necrosis at 4 g/kg. Nephrotoxicity was not significantly exacerbated by pre- or concurrent treatment with probenecid or furosemide/gentamicin. Mice showed evidence of nephrotoxicity only at dose levels of 8 g/kg and higher (single subcutaneous dose).

Ceftazidime has been administered intramuscularly to rats for periods up to three months (900 mg/kg/day top dose) and subcutaneously for periods up to six months (20 mg/kg/day top dose). There was no toxicity at 300 mg/kg, but at higher dose levels in the six-month study there was evidence of treatment-related effects on the kidney and the liver. Mild anemia was also encountered at the higher dose levels.

Dogs have been treated intramuscularly for periods up to three months (500 mg/kg/day top dose) and intravenously for periods up to six months (850 mg/kg/day top dose). There was no evidence of toxicity in the three month intramuscular study. At doses of 600 mg/kg and higher in the six-month intravenous study, there were some changes in the renal tubular epithelium, which electronmicroscopically appear to represent heterolysosomes. No ultrastructural damage was reported.

Since there was some concern about pyridine generated during storage, a mouse micronucleus test was done both on fresh ceftazidime and ceftazidime that had been stored at 25°C for 24 hours; results were negative. Mutagenicity assays (bacterial and mammalian) were negative. A limit on the level of pyridine was set in the monograph.

V. Medical

CONTROLLED CLINICAL EFFICACY TRIALS - ACTIVE DRUG COMPARISONS

Data from fifteen randomized controlled trials were used to compare efficacy and safety.

1. Lower Respiratory Tract Infections with or without Septicemia

a) A randomized controlled multiclinic trial comparing 1.0 g of ceftazidime q 8 h with 1.0 g of cefamandole q 6 h in the treatment of lower respiratory tract infections and/or systemic bacterial septicemia was conducted at nine clinical centers. Two hundred forty-two patients participated in this study. One hundred twenty four patients (87 males and 37 females) received ceftazidime and 118 (80 males and 38 females) received cefamandole. Patients ranged in age from 18 to 95 years. One hundred twelve ceftazidime-treated patients and 99 cefamandole-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 91.0% and was 78.9% for cefamandole. The most commonly isolated pathogens in both groups were E. coli, S. pneumoniae, and Klebsiella species.

Clinical cure or improvement occurred in all evaluable patients in each group. Of these, complete cures were reported for 76 ceftazidime-treated patients (67.9%) and for 53 cefamandole-treated patients (53.5%).

b) Two randomized controlled multiclinic trials to compare 2.0 g of ceftazidime q 8 h and a regimen of tobramycin plus ticarcillin in the treatment of serious lower respiratory tract infections were conducted at ten clinical centers. One hundred forty three patients ranging in age from 19 to 93 years were enrolled. Seventy-three patients (50 males and 23 females) received ceftazidime and 70 patients (40 males and 30 females) received tobramycin plus ticarcillin. Fifty-four ceftazidime-treated patients and 39 tobramycin/ticarcillin-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for the ceftazidime group was 85.5% and the bacteriologic response for the tobramycin/ticarcillin-treated group was 77.4%. The most commonly isolated pathogens in both groups were Klebsiella species, E. coli, and Pseudomonas aeruginosa.

Clinical cure or improvement occurred in 88.9% of the test drug group and 88.2% of the control group. Of these, complete cures were reported for 31 of 54 ceftazidime-treated patients (57.4%) and for 29 of 59 control group patients (53.5%).

c) A randomized controlled, single-clinic trial was conducted comparing 2.0 g of ceftazidime with 2.0 g of moxalactam q 12 h in the treatment of lower respiratory tract infections. Sixteen patients participated in this study. Eight patients (6 males and 2 females) received ceftazidime and eight patients (5 males and 3 females) received moxalactam. Patients ranged in age from 41 to 82 years. Five ceftazidime-treated patients and seven moxalactam-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 100% and was 80% for moxalactam. The most commonly isolated pathogen in both groups was S. pneumoniae.

Clinical cure or improvement occurred in all evaluable patients in each group. Of these, complete cures were reported for all ceftazidime-treated patients and for six moxalactam-treated patients (85.7%).

2. Skin and Skin Structure Infections

a) A randomized controlled multiclinic trial comparing 1.0 g of ceftazidime q 8 h with 1.0 g of cefamandole q 6 h in the treatment of skin and skin structure infections was conducted at ten clinical centers. Two hundred sixty nine patients participated in this study. One hundred thirty seven patients (73 males and 64 females) received ceftazidime and 132 patients (78 males and 54 females) received cefamandole. Patients ranged in age from 18 to 86 years. Eighty-six ceftazidime-treated patients and 67 cefamandole-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 89.8% and was 83.9% for cefamandole. The most commonly isolated pathogens in both groups were S. aureus, P. mirabilis, and P. aeruginosa.

Clinical cure or improvement occurred in 90.7% of evaluable patients in the ceftazidime-treated group and in 92.5% of the cefamandole-treated group. Of these, complete cures were reported for 54 ceftazidime-treated patients (62.8%) and for 38 cefamandole-treated patients (56.7%).

b) A randomized controlled multiclinic trial comparing 2.0 g q 8 h of ceftazidime with a regimen of tobramycin and ticarcillin in the treatment of skin and skin structure infections was conducted at eight clinical centers. One hundred fourteen patient participated in this study. Fifty-nine patients (33 males and 26 females) received ceftazidime and 55 patients (26 males and 29 females) received the tobramycin/ticarcillin regimen. Patients ranged in age from 16 to 89 years. Forty-two ceftazidime-treated patients and 35 tobramycin/ticarcillin-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 90.9% and was 84.4% for the tobramycin/ticarcillin regimen. The most commonly isolated pathogens in both groups were Enterobacter species, S. aureus, and P. aeruginosa.

Clinical cure or improvement occurred in 95.2% of the evaluable ceftazidime-treated patients and in 85.8% of the evaluable patients in the antibiotic-control group. Of these, complete cures were reported for 21 ceftazidime-treated patients (50%) and for 22 control-group patients (62.9%).

c) A randomized controlled two-clinic trial comparing 2.0 g of ceftazidime q 12 h with 2.0 g of moxalactam q 12 h in the treatment of skin and skin structure infections was reported. Fifty-seven patients participated in this study. Twenty-seven patients (15 males and 12 females) received ceftazidime and 30 patients (9 males and 21 females) received moxalactam. Patients ranged in age from 22 to 94 years. Seventeen ceftazidime-treated patients and 20 moxalactam-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 100% and was 95% for moxalactam. The most commonly isolated pathogens in both groups were P. aeruginosa and S. aureus.

Clinical cure or improvement occurred in 88.2% of the ceftazidime-treated patients and in 85% of the moxalactam-treated patients. Of these, complere cures were reported for 13 ceftazidime-treated patients (76.5%) and for 13 moxalactam-treated patients (65%).

3. Gynecological Infections

A randomized controlled two-clinic trial comparing 2.0 g of ceftazidime q 8 h with a regimen of tobramycin plus clindamycin in the treatment of gynecological infections was reported. Seventy female patients, most of whom were diagnosed as having endoparametritis, participated in this study. Forty patients received ceftazidime and forty patients received the control regimen. Patients ranged in age from 15 to 33 years. Thirty-nine patients in each group were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 96.2% and was 91.7% for the tobramycin/clindamycin regimen. The most commonly isolated pathogens in both groups were Bacteroides species (excluding B. fragilis), E. coli, and beta hemolytic streptococci.

Complete cures were reported for 36 ceftazidime-treated patients (92.5%) and for 34 tobramycin/clindamycin-treated patients (87.2%).

4. Intra-Abdominal Infections and Septicemia

a) A randomized controlled single-center trial was conducted to compare 2.0 g of ceftazidime q 8 h with a regimen of tobramycin and clindamycin in the treatment of intra-abdominal infections. Fourteen patients participated in this study. Six patients (3 males and 3 females) received ceftazidime and eight patients (5 males and 3 females) received the control regimen. Patients ranged in age from 49 to 79 years. All patients were evaluated for clinical efficacy; all were considered in assessing safety.

Three evaluable pathogens in the ceftazidime-treated group were eradicated and four of five evaluable pathogens in the control group were eradicated. Isolated pathogens in both groups were Klebsiella species and E. coli.

Clinical cure or improvement occurred in five of the six ceftazidime-treated patients and in six of the eight control group patients. Complete clinical cures were reported for three patients in each group.

b) A randomized controlled single-clinic study was conducted to compare 2.0 g of ceftazidime q 8 h with a regimen of tobramycin and clindamycin in the treatment of surgical infections. Fifty-seven patients participated in this study. Thirty-five patients (24 males and 11 females) received ceftazidime and 22 patients (13 males and 9 females) received the tobramycin/clindamycin regimen. Patients ranged in age from 17 to 71 years. Eighteen ceftazidime-treated patients and nine control patients were evaluated for clinical efficacy; all were considered in assessing safety.

Five qualified isolates were eradicated, three in the ceftazidime group and two in the control group.

Complete clinical cures were reported for 14 of 18 ceftazidime-treated patients (77.8%) and for seven of nine tobramycin/clindamycin-treated patients (77.8%).

c) A randomized controlled single-clinic trial was conducted comparing 2.0 g of ceftazidime q 8 h with a regimen of tobramycin and clindamycin in the treatment of serious intra-abdominal infections. Sixty-seven patients participated in this study. Thirty-four patients (16 males and 18 females) received ceftazidime and 33 patients (18 males and 15 females) received the control regimen. Patients ranged in age from 18 to 89 years. Thirty-three ceftazidime-treated patients and 32 tobramycin/clindamycin-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 98.7% and was 71.5% for the control regimen. The most commonly isolated pathogens in both groups were E. coli and Bacteroides species, including B. fragilis.

Clinical cure or improvement occurred in all evaluable patients in the ceftazidime-treated group and in 87.5% of the control group. Of these, complete cures were reported for 25 ceftazidime-treated patients (71.8%) and for 15 tobramycin/clindamycin-treated patients (46.9%).

5. Urinary Tract Infections

a) A randomized controlled multiclinic trial comparing one gram of ceftazidime per day with 3.0 g of tobramycin per day in the treatment of complicated urinary tract infections was conducted at five clinical centers. One hundred eighty-six patients participated in this study. Ninety-six patients (64 males and 32 females) received ceftazidime and 90 patients (64 males and 26 females) received tobramycin. Patients ranged in age from 20 to 94 years. Sixty-seven ceftazidime-treated patients and 55 tobramycin-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 85.3% and was 91.7% for tobramycin. The most commonly isolated pathogens in both groups were P. aeruginosa, E. coli, and Klebsiella species.

Clinical cure or improvement occurred in all evaluable patients in the ceftazidime group and in 94.5% of evaluable patients in the tobramycin group. Of these, complete cures were reported for 51 ceftazidime-treated patients (76.1%) and for 39 tobramycin-treated patients (70.9%).

6. Bone and Joint Infections

A randomized controlled multiclinic trial comparing 2.0 g of ceftazidime q 12 h with a regimen of tobramycin and ticarcillin in the treatment of bone and joint infections was conducted at four clinical centers. Nineteen patients participated in this study. Twelve patients (10 males and 2 females) received ceftazidime and seven patients (4 males and 3 females) received the control regimen. Patients ranged in age from 18 to 65 years. Eleven ceftazidime-treated patients and seven tobramycin/ticarcillin-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 92.3% and was 100% for the tobramycin/ticarcillin-treated group. The most commonly isolated pathogen in both groups was Pseudomonas aeruginosa.

Clinical cure or improvement occurred in all evaluable patients in each group. Of these, complete cures were reported for 6 ceftazidime-treated patients (54.5%) and for all seven tobramycin/ticarcillin-treated patients.

7. Serious Gram-Negative Infections

A randomized controlled multiclinic trial comparing 2.0 g of ceftazidime q 8 h with 2.0 g of moxalactam q 8 h in the treatment of serious gram-negative infections was conducted at five clinical centers. Eighty-one patients participated in this study. Forty-two patients (25 males and 17 females) received ceftazidime and 39 patients (27 males and 12 females) received moxalactam. Patients ranged in age from 17 to 87 years. Forty ceftazidime-treated patients and 37 moxalactam-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety. The 77 evaluable patients were diagnosed as having complicated urinary tract infections (24 patients), uncomplicated urinary tract infections (22 patients), bacterial septicemia (14 patients), respiratory tract infections (13 patients), intra-abdominal infections (2 patients), and miscellaneous infections (2 patients).

The bacteriological response for ceftazidime was 95.4% and was 91.7% for moxalactam. The most commonly isolated pathogen in both groups was E. coli.

Clinical cure or improvement occurred in all evaluable patients in each group. Of these, complete cures were reported for 39 ceftazidime-treated patients (97.5%) and for 32 moxalactam-treated patients 86.5%).

8. Central Nervous System Infections

A randomized controlled single-clinic trial was conducted comparing ceftazidime in doses of 50 mg/kg q 8 h with a regimen of ampicillin and chloramphenicol in the treatment of bacterial meningitis in infants and children. Seventy-four patients participated in this study. Forty-seven patients (28 males and 19 females) received ceftazidime and 27 patients (19 males and 8 females) received the ampicillin/chloramphenicol regimen. Patients ranged in age from one month to 15 years. Thirty-seven ceftazidime-treated patients and 20 ampicillin/chloramphenicol-treated patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 96.2% and was 100% for the control group. The most commonly isolated pathogens in both groups were H. influenzae and N. meningitidis.

Clinical cure or improvement occurred in all 36 of the 37 evaluable patients in the ceftazidime-treated group and in 21 of the 23 patients in the control group. Of these, complete cures were reported for 35 ceftazidime-treated patients (94.6%) and for 20 of the ampicillin/chloramphenicol-treated patients (87%).

9. Bacterial Septicemia

Concurrent bacterial septicemia was diagnosed in 151 patients participating in randomized controlled trials. Of these, 77 isolates from ceftazidime-treated patients were qualified for evaluation and 48 isolates from patients treated with control regimens were qualified for evaluation. There was a 99.2% cure rate.

SUPPORTIVE CONTROLLED CLINICAL EFFICACY TRIALS: CEFTAZIDIME DOSE COMPARISONS

1. Lower Respiratory Tract Infections

A randomized controlled multiclinic trial comparing ceftazidime in a dose of 0.5 g q 8 h with a dose of 1.0 g q 8 h in the treatment of acute lower respiratory tract infections was conducted at five clinical centers. One hundred ninety eight patients participated in this study. Ninety-seven patients (54 males and 43 females) received 0.5 gram doses and 101 patients (58 males and 43 females) received 1.0 gram doses. Patients ranged in age from 15 to 99 years. Eighty-four 0.5 gram group patients and 81 one-gram group patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for the lower dose was 93% and 95.5% for the one-gram dose group. The most commonly isolated pathogens in both groups were S. pneumoniae, E. coli, Klebsiella species, and P. aeruginosa.

Clinical cure or improvement occurred in 82 of 84 patients in the one-half gram dose group and in 74 of 81 patients in the one-gram dose group. Of these, complete cures were reported for 58 patients in the one-half gram dose group (69%) and for 54 patients in the one-gram dose group (66%).

2. Skin and Skin Structure Infections

A randomized controlled multiclinic trial comparing ceftazidime in doses of 0.5 g q 8 h with doses of 1.0 g q 8 h in the treatment of skin and skin structure infections was conducted at six clinical centers. Two hundred fourteen patients participated in this study. One hundred six patients (60 males and 46 females) received 0.5-gram doses and 108 patients (61 males and 47 females) received one-gram doses. Patients ranged in age from 17 to 98 years. Seventy-eight 0.5-gram group patients and 78 one-gram group patients were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for the 0.5-gram dose was 85.1% and 93.8% for the one-gram dose. The most commonly isolated pathogens in both groups were S. aureus, S. pyogenes, Pseudomonas aeruginosa, and P. mirabilis.

Clinical cure or improvement occurred in all but one evaluable patient in each group. Of these, complete cures were reported for 61 of 78 one-half gram dose patients (78.2%) and for 52 of 78 one-gram dose patients (66.7%).

3. Urinary Tract Infections

Randomized controlled multiclinic trials comparing 0.25g, 0.5 g, and 1.0 g of ceftazidime q 12 h in the treatment of uncomplicated or complicated urinary tract infections were conducted at four clinical centers. Ceftazidime was given intramuscularly in one multiclinic study and intravenously in the other. One hundred sixty six patients participated. Fifty three patients (24 males and 29 females) received the 0.25 gram dose, 58 patients (28 males and 30 females) received the 0.5 gram dose, and 55 patients (23 males and 32 females) received the 1.0 gram dose. Patients ranged in age from 18 to 88 years. Forty-five patients in the 0.25 gram group, 45 patients in the 0.5 gram group, and 44 patients in the one-gram group were evaluated for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological responses were 88.9% for the 0.25 gram dose, 97.5% for the 0.5 gram dose, and 87.2% for the one-gram dose. The most commonly isolated pathogens in all groups were E. coli, P. mirabilis, and P. aeruginosa.

Complete cures were reported for 35 patients treated with 0.25 gram (77.8%), for 40 patients treated with 0.5 gram (88.9%), and for 35 patients treated with one gram (79.5%).

UNCONTROLLED EFFICACY TRIALS

1. Lower Respiratory Tract Infections

Lower respiratory tract infections were reported in ten uncontrolled trials of ceftazidime at 26 clinical centers. One hundred seventy-nine patients of all ages, including neonates, participated in these studies. There were 159 patients who were evaluable for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response was 90%. The most commonly isolated pathogens were Pseudomonas aeruginosa, H. influenzae, Klebsiella species, and S. pneumoniae.

Clinical cure or improvement occurred in 149 evaluable patients (93.7%). Of these, complete cures were reported for 115 patients (72.3%).

2. Skin and Skin Structure Infections

Skin and skin structure infections were reported in twelve uncontrolled trials of ceftazidime at 25 clinical centers. One hundred seventeen patients of all ages, including infants, participated in these studies. There were 108 patients who were evaluable for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response was 91.4%. The most commonly isolated pathogen was Pseudomonas aeruginosa.

Clinical cure or improvement occurred in 102 of the evaluable patients (94.5%). Of these, complete cures were reported for 68 patients (63%).

3. Urinary Tract Infections

Complicated and uncomplicated urinary tract infections were reported in eleven uncontrolled trials of ceftazidime at 19 clinical centers. One hundred sixty-five patients of all ages, including infants, received ceftazidime. One hundred two patients were evaluable for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response was 87.5%. The most commonly isolated pathogens were Pseudomonas aeruginosa, E. coli, and Klebsiella species.

Clinical cure or improvement occurred in all evaluable patients except one. Of these, complete cures were reported for 80 patients (78.4%).

4. Bone and Joint Infections

Bone and joint infections were reported in nine uncontrolled trials of ceftazidime at 18 clinical centers. Ninety-three patients of all ages participated in these studies. Eighty-seven patients were evaluable for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response for ceftazidime was 94.4%. The most commonly isolated pathogens were Pseudomonas aeruginosa and S. aureus.

Clinical cure or improvement occurred in 85 evaluable patients (97.7%). Of these, complete cures were reported for 54 patients (62.1%).

5. Bacterial Septicemia

Bacterial septicemia was reported in fourteen uncontrolled trials of ceftazidime at 29 clinical centers. One hundred forty five patients of all ages participated in these studies.

Thirty-seven cases were evaluated for bacteriological efficacy. The bacteriological response was 100%. The most commonly isolated pathogen was E. coli.

One hundred sixteen cases were evaluated for clinical efficacy. Clinical cure or improvement occurred in 113 evaluable patients (97.4%). Of these, complete cures were reported for 93 patients (80.2%).

6. Intra-Abdominal Infections

Intra-abdominal infections were reported in seven uncontrolled trials of ceftazidime at 11 clinical centers. Twenty-four patients participated in these studies. Twenty-one patients were evaluable for bacteriological and clinical efficacy; all were considered in assessing safety.

The bacteriological response was 93.3%. The most commonly isolated pathogen was E. coli.

Clinical cure or improvement occurred in 18 evaluable patients (85.7%) Of these, complete cures were reported for 12 patients (57.1%).

7. Central Nervous System Infections

Central nervous system infections were reported in two uncontrolled trials of ceftazidime at five clinical centers. Fourteen patients participated in these studies. Two patients were evaluable for bacteriological efficacy and both were cured. H. influenzae was eradicated in each case.

Thirteen patients were evaluated for clinical efficacy. Clinical cure or improvement occurred in twelve patients (92.3%). Of these, complete cures were reported for ten patients (76.9).

PEDIATRIC EFFICACY STUDIES

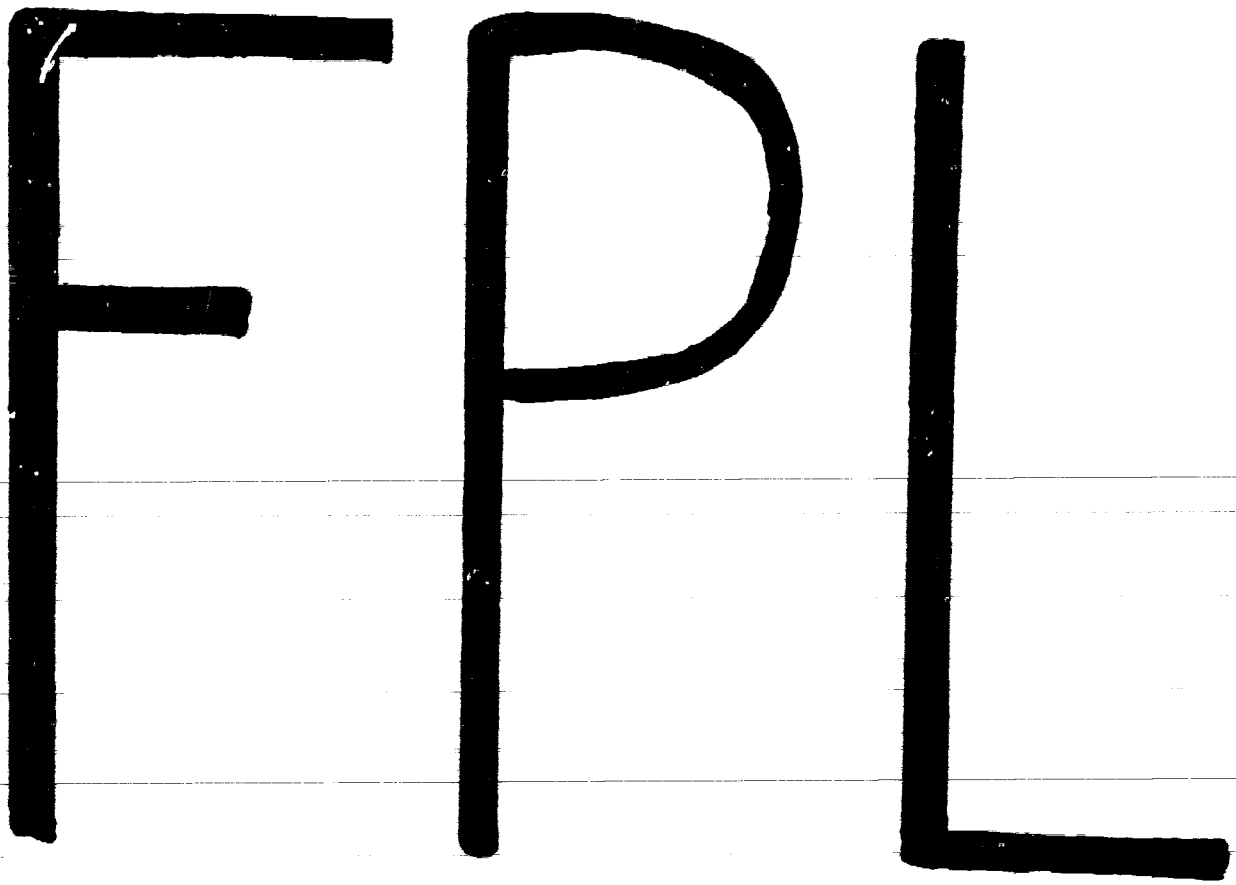
Pediatric patients were included in four randomized controlled trials comparing ceftazidime with another treatment regimen in the treatment of skin and skin structure infections (4 pts.), in the treatment of febrile granulocytic disorders (24 pts. in two studies), and in the treatment of gram-negative infections (30 pts.). Uncontrolled trials of ceftazidime in the treatment of lower respiratory tract infections (17 pts.), skin and skin structure infections (52 pts.), and acute serious infections (7 pts.) in pediatric patients were reported. An additional 78 infants and young children with infections were treated with ceftazidime in pharmacokinetic trials.

SAFETY EVALUATION

In these studies, drug safety was evaluated in 2648 patients who received ceftazidime and 1051 patients who received the control regimens. Of these, 198 ceftazidime-treated patients, or 7.5%, experienced one or more adverse events during the course of treatment. In 37 patients, the adverse events were attributed to a cause other than ceftazidime. In the remaining 161 patients, 6.1%, the cause of the event was unknown and was possibly or probably drug related. Adverse events were generally minor and were limited to (1) local reactions such as phlebitis or skin inflammation at the site of the injection, (2) hypersensitivity reactions such as rash and pruritis, (3) gastro-intestinal symptoms such as diarrhea or abdominal pain, and (4) rarely, central nervous system involvement such as headache. The incidence of any one of these events was 2% or less.

The most frequent adverse reactions were reactions at the site of the injection, diarrhea, rash, and nausea. Some other reactions, seen less than 0.5% of the time, were headache, pyrexia, and itching. The most frequent abnormal laboratory findings with ceftazidime were eosinophilia and elevated liver enzymes.

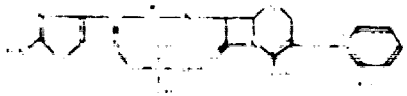
Treatment was discontinued in 50 ceftazidime-treated patients, 1.9%, because of adverse reactions. There were 89 deaths during or shortly after treatment with ceftazidime. In each case death was attributed to the severe underlying condition in very sick patients. In no instance was ceftazidime implicated as a factor in the cause of death.


FPL

(ceftazidime for injection, Glaxo)

For intravenous or intramuscular use

DESCRIPTION Ceftazidime is a semisynthetic broad spectrum beta-lactam antibiotic for parenteral administration It is the pentahydrate of Pyridinium 1 [[7 [[(2 amino 4 thiazolyl) (carboxy 1 methylethoxy)imino]acetyl]amino] 2 carboxy 8 oxo 5 thia 1 azabicyclo[4 2 0]oct 2 en 3 yl]methyl] hydroxide inner salt [6R [6α 7[Z]]] It has the following structure



FORTAZ® (ceftazidime for injection Glaxo) is a sterile dry powdered mixture of ceftazidime pentahydrate and sodium carbonate The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution The total sodium content of the mixture is approximately 54 mg (2 3 mEq/g of ceftazidime activity Solutions of FORTAZ range in color from light yellow to amber depending upon the diluent and volume used The pH of freshly constituted solutions usually ranges from 5 0 to 8 0

CLINICAL PHARMACOLOGY After intravenous administration of 500 mg and 1 g doses of ceftazidime over five minutes to normal adult male volunteers mean peak serum concentrations of 45 mcg/ml and 90 mcg/ml respectively were achieved After intravenous infusion of 500 mg 1 g and 2 g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers mean peak serum concentrations of 42 mcg/ml 69 mcg/ml and 170 mcg/ml respectively were achieved The average serum concentrations following intravenous infusion of 500 mg 1 g and 2 g doses to these volunteers over an eight hour interval are given in Table 1

Table 1

Ceftazidime IV Dosage	Serum Concentrations (mcg/ml)				
	0.5 hr	1 hr	2 hr	4 hr	8 hr
500 mg	42	25	12	6	2
1 g	60	38	23	11	3
2 g	179	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following intravenous administration was approximately 1.9 hours Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple intravenous doses of 1 g and 2 g every eight hours for ten days.

Following intramuscular administration of 500 mg and 1 g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 mcg/ml and 39 mcg/ml respectively at approximately one hour. Serum concentrations remained above 4 mcg/ml for six and eight hours after the intramuscular administration of 500 mg and 1 g doses, respectively. The half-life of ceftazidime in these volunteers was approximately two hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every eight hours for five days Therefore, a dosage adjustment from the normal recommended dosage regimen is not necessary in patients with impaired liver function

Ceftazidime is not metabolized systemically and is excreted entirely by the kidneys Approximately 80% to 90% of the dose is recovered in the urine within 24 hours following 500 mg 1 g and 2 g doses Urinary concentrations of ceftazidime are very high following administration of these doses Urinary concentrations of ceftazidime greater than 1000 mcg/ml were maintained for four to six hours following 500 mg and 1 g doses and for eight hours following 2 g doses

Ceftazidime is excreted by glomerular filtration into the urine Tubular secretion is negligible

MICROBIOLOGY Ceftazidime has in vitro activity against a wide range of gram-negative and gram-positive bacteria Ceftazidime is bactericidal in action Its bactericidal activity results from inhibition of biosynthesis of cell wall mucopeptide Ceftazidime is stable in the presence of beta-lactamases both penicillinase and cephalosporinase of gram-negative and gram-positive bacteria and is effective against bacteria resistant to penicillins cephalosporins and aminoglycosides due to beta-lactamase mediated hydrolysis

Ceftazidime has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of this package insert

Pseudomonas aeruginosa (formerly *Pseudomonas aeruginosa*) *Proteus mirabilis* *Proteus morganii* (formerly *Proteus morganii*) *Proteus vulgaris* *Providencia rettgeri* (formerly *Proteus rettgeri*) *Acinetobacter* species *Salmonella* species *Citrobacter* species *Klebsiella* species including *Klebsiella pneumoniae* *Enterobacter* species *Serratia* species including *Serratia marcescens* *Pseudomonas cepacia* (formerly *Pseudomonas cepacia*) *Pseudomonas maltophilia* (formerly *Xanthomonas maltophilia*) *Pseudomonas pseudomallei* *Haemophilus influenzae* including ampicillin resistant strains *Haemophilus parainfluenzae* *Neisseria gonorrhoeae* *Neisseria meningitidis* *Yersinia enterocolitica* *Yersinia pestis* *Pasteurella multocida* *Streptococcus agalactiae* (Group B streptococci) *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*) *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) *Staphylococcus aureus* (methicillin susceptible strains) *Staphylococcus epidermidis* (methicillin susceptible strains) *Staphylococcus saprophyticus* (methicillin susceptible strains) *Streptococcus bovis* (formerly *Streptococcus bovis*) *Streptococcus sanguis* (formerly *Streptococcus sanguis*) *Streptococcus salivarius* (formerly *Streptococcus salivarius*) *Streptococcus mitis* (formerly *Streptococcus mitis*) *Streptococcus mutans* (formerly *Streptococcus mutans*) *Peptococcus* species *Peptostreptococcus* species *Bacteroides fragilis* *Bacteroides* species including *Bacteroides melaninogenicus* (formerly *Bacteroides melaninogenicus*) *Clostridium* species including *Clostridium perfringens* *Clostridium difficile* *Fusobacterium* species *Propionibacterium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species *Neisseria gonorrhoeae* *Haemophilus parainfluenzae* *Yersinia enterocolitica* and *Shigella* species

Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against *P aeruginosa* and the *Enterobacteriaceae* Ceftazidime and carbenicillin have also been shown to be synergistic *in vitro* against *P aeruginosa*

Ceftazidime is not active *in vitro* against methicillin resistant staphylococci *Streptococcus faecalis* and many other enterococci *Listeria monocytogenes* *Campylobacter* species or *C difficile*

Susceptibility Tests 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 ceftazidime

Reports from the laboratory giving results of the standard single disk susceptibility test with a 30 mcg ceftazidime disk should be interpreted according to the following criteria

Susceptible organisms produce zones of 18 mm or greater indicating that the test organism is likely to respond to therapy

Organisms that produce zones of 15 mm to 17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (eg urine) in which high antibiotic levels are attained

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used

Standardized procedures require the use of laboratory control organisms The 30 mcg ceftazidime disk should give zone diameters between 25 mm and 32 mm for *E coli* ATCC 25922 For *P aeruginosa* ATCC 27853 the zone diameters should be between 22 mm and 29 mm For *S aureus* ATCC 25923 the zone diameters should be between 16 mm and 20 mm

In other susceptibility testing procedures, eg, tCS agar dilution or the equivalent, a bacterial isolate may be considered susceptible if the MIC value for ceftazidime is not more than 16 mcg/ml Organisms are considered resistant to ceftazidime if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml but greater than 16 mcg/ml are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms Standard ceftazidime powder should give MIC values in the range of 4 mcg/ml and 16 mcg/ml for *S aureus* ATCC 25923 For *E coli* ATCC 25922 the MIC range should be between 0 125 mcg/ml and 0 5 mcg/ml For *P aeruginosa* ATCC 27853 the MIC range should be between 0 5 mcg/ml and 2 mcg/ml

INDICATIONS AND USAGE FORTAZ® (ceftazidime for injection Glaxo) is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the diseases listed below

1. **Lower Respiratory Tract Infections**, including pneumonia caused by *P aeruginosa* and other *Pseudomonas* species, *H influenzae*, including ampicillin resistant strains *Klebsiella* species, *Enterobacter* species, *P mirabilis*, *E coli*, *Serratia* species, *Citrobacter* species, *S pneumoniae*, and *S aureus* (methicillin susceptible strains)

Tissue or Fluid	Dose Route	No Patients	Time of Sample Post dose	Average Tissue or Fluid Level (mcg/ml
Urine	500 mg IM	6	0-2 hrs	2 100
	2 g IV	6	0-2 hrs	12 000
Bile	2 g IV	3	90 min	36 4
Synovial fluid	2 g IV	13	2 hrs	25 6
Peritoneal fluid	2 g IV	8	2 hrs	48 1
Sputum	1 g IV	8	1 hr	9
Cerebrospinal fluid uninflamed	2 g q8h IV	5	1/2 min	9 6
meninges	2 g q8h IV	4	180 min	9 4
Aqueous humor	2 g IV	13	1-3 hrs	1
Blister fluid	1 g IV	7	2-3 hrs	19
Lymphatic fluid	1 g IV	7	2-3 hrs	23
Bone	2 g IV	8	0 6-7 hr	3 1 1
Heart muscle	2 g IV	36	30 180 min	12
Skin	2 g IV	22	30 180 min	6 6
Skeletal muscle	2 g IV	35	30 280 min	9 4
Myometrium	2 g IV	31	1 2 hrs	18 7

Microbiology Ceftazidime is bactericidal in action exerting its effect by inhibition of enzymes responsible for cell wall synthesis. A wide range of gram-negative organisms are susceptible to ceftazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In addition ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases plasmid or chromosomal which are produced by both gram-negative and gram-positive organisms and consequently is active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime has been shown to be active against the following organisms both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**):

Aerobes, Gram-Negative: *Pseudomonas* species including *Pseudomonas aeruginosa*; *Klebsiella* species including *Klebsiella pneumoniae*; *Proteus mirabilis*; *Proteus vulgaris*; *Escherichia coli*; *Enterobacter* species including *Enterobacter cloacae* and *Enterobacter aerogenes*; *Citrobacter* species including *Citrobacter freundii* and *Citrobacter diversus*; *Serratia* species; *Haemophilus influenzae*, including ampicillin-resistant strains; and *Neisseria meningitidis*.

Aerobes, Gram-Positive: *Staphylococcus aureus* including penicillinase- and non-penicillinase-producing strains; *Streptococcus pyogenes* (group A beta-hemolytic streptococci); *Streptococcus agalactiae* (group B streptococci); and *Streptococcus pneumoniae*.

Anaerobes: *Bacteroides* species (NOTE: many strains of *Bacteroides fragilis* are resistant).

Ceftazidime has also been shown to demonstrate *in vitro* activity against the following microorganisms, although its

[illegible]

Specimen for bacterial cultures should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

FORTAZ may be used alone in cases of confirmed or suspected sepsis. FORTAZ has been used successfully in clinical trials in empiric therapy in cases where various concomitant therapy with other antibiotics have been used.

FORTAZ may also be used concomitantly with other antibiotics such as aminoglycosides or vancomycin, and clindamycin in severe mixed bacterial infections, and in the immunocompromised patient. When such concomitant therapy is appropriate, the dosage, route of administration and scheduling for the other antibiotic should be determined by the drug's characteristics, the severity of the infection and the patient's condition.

CONTRAINDICATIONS: FORTAZ is contraindicated in patients who have shown hypersensitivity to cefta-dime or the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH FORTAZ IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PATIENTS WITH TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. IF AN ALLERGIC REACTION TO FORTAZ OCCURS, DISCONTINUE TREATMENT WITH 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 alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C. difficile* is one primary cause of antibiotic-associated colitis.

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 of colitis should also be considered.

PRECAUTIONS: FORTAZ has not been shown to be nephrotoxic, however, because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage

Tear Away

FORTAZ®

(ceftazidime for injection, Glaxo)

Instructions for Constitution

Vials: 500 mg IM/IV
1 g IM/IV
2 g IV

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution will be obtained in 1-2 minutes.
3. Invert the vial. Ensuring that the syringe plunger is fully depressed, insert the needle through the vial closure and withdraw the required amount of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution as it does not enter the headspace. The withdrawn solution may contain some bubbles of carbon dioxide.

Note: As with the administration of all parenteral products, air bubbles should be expressed from the syringe immediately prior to injection of Fortaz®.

Infusion Pack: 1 g, 2 g

1. Insert the syringe needle through the vial closure and inject the diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.

should be reduced when ceftazidime is administered to such patients (see **DOSAGE AND ADMINISTRATION**). Concomitant dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organism(s).

As with other antibiotics, prolonged use of FORTAZ (ceftazidime for injection, Glaxo) may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

FORTAZ should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity and ototoxicity were not noted when FORTAZ was given alone in clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an Ames test were both negative for mutagenic effects.

Usage in Pregnancy: ***Pregnancy Category B:*** Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to FORTAZ. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when FORTAZ is administered to a nursing woman.

ADVERSE REACTIONS: FORTAZ® is generally well tolerated. The incidence of adverse reactions associated with the administration of FORTAZ was low in clinical trials. The most common were local reactions following intravenous injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiram-like reactions were reported. The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects, reported in less than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Hypersensitivity Reactions, reported in 2% of patients were pruritus, rash, and fever. Immediate hypersensitivity reactions occurred in 1 in 285 patients.

Gastrointestinal Symptoms, reported in less than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500) and abdominal pain (1 in 416).

Less Frequent Adverse Events (less than 1%) were convulsions and reversible central nervous system events which included headache, dizziness, and paresthesia.

Laboratory Test Changes noted during FORTAZ clinical trials were transient and included: eosinophilia (1 in 13), positive Coombs test without hemolysis (1 in 23), thrombocytosis (1 in 45); and slight elevations in one or more of the hepatic enzymes: SGOT (1 in 18), SGPT (1 in 15), LDH (1 in 18) and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, thrombocytopenia, and lymphocytosis were seen very rarely.

DOSAGE AND ADMINISTRATION: Dosage: The usual adult dosage is 1 g administered intravenously or intramuscularly every eight or 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The guidelines for dosage of FORTAZ® are listed in Table 3. The following dosage schedule is recommended:

Table 3: Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dose	1 g IV or IM	q8-12h
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 g IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8-12h
Uncomplicated pneumonia, mild skin and skin structure infections	500 mg-1 g IV or IM	q8h
Serious gynecological and intra-abdominal infections	2 g IV	q8h
Meningitis	2 g IV	q8h
Very severe life-threatening infections, especially in patients who are immunocompromised	2 g IV	q8h

Pediatric Patients (over 2 months of age): The usual dosage is 30 to 50 mg/kg administered intravenously or intramuscularly every eight hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

Neonates and Infants (up to 2 months of age): The usual dosage is 25 to 60 mg/kg administered intravenously every 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

Patients with Impaired Renal Function: Dosage must be adjusted in patients with renal impairment. Following a loading dose of 1 g, maintenance dosage should be reduced in proportion to the severity of renal impairment. Dosage should be adjusted on the basis of creatinine clearance as follows:

Creatinine Clearance (ml/min)	Dose	Frequency
50-31	1 g	q12h
30-16	1 g	q24h
15-6	500 mg	q24h
<5	500 mg	q48h

Patients Undergoing Hemodialysis: Following a loading dose of 1 g, maintenance dosage should be administered only after dialysis when the patient is undergoing hemodialysis. On dialysis days, 500 mg every 24 hours is recommended.

Patients Undergoing Peritoneal Dialysis: Following a loading dose of 1 g, maintenance dosage should be 500 mg every 48 hours.

Patients Undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD): In such patients, a loading dose of ceftazidime 1 g may be given, followed by 500 mg every 24 hours in addition to intravenous use. FORTAZ (ceftazidime for injection, Glaxo) can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

NOTE: Generally, FORTAZ should be continued for two days after the signs and symptoms of infection have disappeared but in complicated infections longer therapy may be required.

Administration: FORTAZ may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Intramuscular Administration: For intramuscular administration, FORTAZ should be constituted with one of the following diluents: Sterile Water for Injection, Bacteriostatic Water for Injection, 0.5% or 1.0% Lidocaine Hydrochloride Injection. Refer to Table 5.

Intravenous Administration: The IV route is preferable for patients with bacterial septicemia, bacterial meningitis, peritonitis 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 pending.

For direct intermittent intravenous administration, constitute FORTAZ as directed in Table 5 with Sterile Water for Injection. Slowly inject directly into the vein over a period of three to five minutes or give through the tubing of an administration set while the patient is also receiving one of the compatible intravenous fluids (see **COMPATIBILITY AND STABILITY**).

For intravenous infusion, constitute the 1 g or 2 g Infuse-Pack with 100 ml Sterile Water for Injection or one of the compatible intravenous fluids listed under the **COMPATIBILITY AND STABILITY** section. Alternatively, constitute the 500 mg, 1 g or 2 g vial and add an appropriate quantity of the resulting solution to an IV container with one of the compatible intravenous fluids.

Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable to discontinue the other solution.

Table 5: Preparation of FORTAZ Solutions

Size	Amount of Diluent to be Added (ml)	Approximate Available Volume (ml)	Approximate Ceftazidime Concentration (mg/ml)
Intramuscular			
500 mg vial	1.5	1.8	280
1 g vial	3.0	3.6	280
Intravenous			
500 mg vial	5	5.3	100
1 g vial	10	10.6	100
2 g vial	10	11.2	180
Infusion Pack			
1 g vial	100*	100	10
2 g vial	100*	100	20
Pharmacy Bulk Package			
6 g vial	26	30	200

*Note: Addition should be in two stages (see Instructions for Constitution).

All vials of FORTAZ as supplied are under reduced pressure. When FORTAZ is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use, please follow the recommended technique of constitution described on the detachable Instructions for Constitution section of this insert.

Solutions of FORTAZ, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential inactivation.

However, if concurrent therapy with FORTAZ and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

COMPATIBILITY AND STABILITY: Intramuscular: FORTAZ®, when constituted as directed with Sterile Water for Injection, Bacteriostatic Water for Injection, or 0.5% or 1% Lidocaine Hydrochloride Injection, maintains satisfactory potency for 18 hours at room temperature or for seven days under refrigeration. Solutions in Sterile Water for Injection that are frozen immediately after constitution in the original container are stable for three months when stored at -20°C. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to eight hours at room temperature or for four days in a refrigerator.

Intravenous: FORTAZ, when constituted as directed with Sterile Water for Injection, maintains satisfactory potency for 18 hours at room temperature or for seven days under refrigeration. Solutions in Sterile Water for Injection in the original container or in 0.9% Sodium Chloride Injection in Viaflex® small volume containers that are frozen immediately after constitution are stable for three months when stored at -20°C. For larger volumes where it may

- Although clinical improvement has been shown bacteriological cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis
- The higher dose should be reserved for immunocompromised children or children with cystic fibrosis or meningitis

Impaired Hepatic Function No adjustment in dosage is required for patients with hepatic dysfunction

Impaired Renal Function Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore in patients with impaired renal function (CrCl < 50 ml/min) it is recommended that the dosage of ceftazidime be reduced to compensate for its slower elimination. In patients with suspected renal insufficiency an initial loading dose of 1 g of ceftazidime may be given. An estimate of CrCl should be made to determine the appropriate maintenance dose. The recommended dosage is presented in Table 1.

Table 1. Recommended Maintenance Doses of FORTAZ® in Renal Insufficiency

Creatinine Clearance (ml/min)	Recommended Unit Dose of Ceftazidime	Frequency of Dosing
50-31	1 g	q12h
30-16	1 g	q24h
15-6	500 mg	q24h
< 5	500 mg	q48h

When only serum creatinine is available the following formula ("Cockcroft's equation") may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age (years)})}{72 \times \text{serum creatinine (mg/dl)}}$$

Females:

0.85 × above value

In patients with severe infections who would normally receive 6 g of ceftazidime daily when it was the renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency increased as appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection and susceptibility of the causative organism.

In children as for adults the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 g is recommended, followed by 1 g after each hemodialysis period.

FORTAZ can also be used in patients undergoing intra-

Injection, M.G. Sodium Lactate Injection, Ringer's Injection, USP, Lactated Ringer's Injection, 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 10% Dextrose Injection, 10% Invert Sugar in Water for Injection and Ringer's-M in 5% Dextrose Injection.

FORTAZ is less stable in Sodium Bicarbonate Injection than in other intravenous fluids and is not recommended as a diluent. Solutions of FORTAZ in 5% Dextrose and 0.9% Sodium Chloride Injection are stable for at least 24 hours at room temperature or 96 hours if refrigerated in plastic infusion bag chambers and volume control devices or plastic intravenous infusion sets.

Ceftazidime at a concentration of 4 mg/ml has been found compatible for 24 hours at room temperature or seven days under refrigeration in 0.9% Sodium Chloride Injection when admixed with Cefuroxime sodium (Zinacef®) 3 mg/ml, Heparin 10 units/ml or 50 units/ml and Potassium Chloride 10 mEq/l or 40 mEq/l.

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

As with other cephalosporins, FORTAZ powder as well as solutions tend to darken depending on storage conditions within the stated recommendations, however product potency is not adversely affected.

HOW SUPPLIED FORTAZ® in the dry state should be stored at controlled room temperature 15° to 30°C (59° to 86°F), and protected from light. FORTAZ is a dry, white to off-white powder supplied in vials and infusion packs as follows:

NDC 0173-0377-31 *500 mg Vials (Tray of 25)
NDC 0173-0378-35 *1 g Vials (Tray of 25)
NDC 0173-0379-34 *2 g Vials (Tray of 10)
NDC 0173-0380-32 *1 g Infusion Pack (Tray of 10)
NDC 0173-0381-32 *2 g Infusion Pack (Tray of 10)
NDC 0173-0382-37 *6 g Pharmacy Bulk Package (Tray of 6)

*equivalent to anhydrous ceftazidime

REFERENCES 1. Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by a standardized single disc method. *Am J Clin Pathol* 1966;45:493. 2. National Committee for Clinical Laboratory Standards. Approved Standard Performance Standards for Antimicrobial Disc Susceptibility Tests (M2-A3). December, 1984. 3. Standardized disc susceptibility test. *Federal Register* 1974;39(May 30):19182-19184. 4. Cockcroft DW and Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709 July 1985

Tear Away

...ill be obtained in 1-2 minutes.
...vial closure to relieve the internal
...on, add the remaining 90 ml of
...and syringe needle, shake the vial
...ssay.
...s important that a gas relief needle
...osure before the product has

...vial closure and inject 26 ml of
...of the diluent. Remove the

...taining approximately 1 g cef-
...ained in 1-2 minutes.
...vial closure to relieve the internal
...e before extracting any solution.

...important that a gas relief needle
...osure before the product has

July 1985

...7709
...eserved.

MED

REV

from FBS

December 14, 1984

MEDICAL OFFICER'S REVIEW OF ANTIBIOTIC FORM 50-578

Initial 227-Volume Submission Dated May 20, 1983,
11-Volume Amendment Dated June 8, 1984,
and 54 Amendments through December 11, 1984

Applicant: Glaxo, Inc. MOR #1
Research Triangle Park, NC

Name of Drug: Generic: Ceftazidime for injection (Ceftazidime pentahydrate)

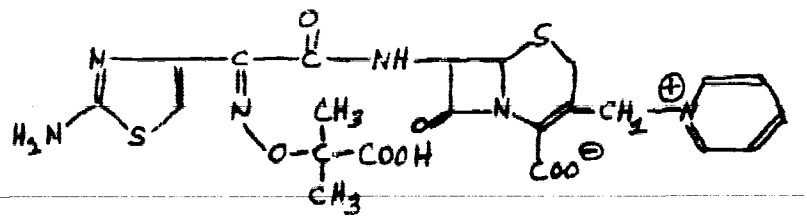
Trade: FORTAZ™

Code: GR 20263

Empirical: $C_{22}H_{32}N_6O_{12}S_2$ Mol Wt. 636.6

Chemical: (6R, 7R)-7-[(z)-2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yloxyimino) acetamido]-3-(1-pyridinium-methyl) ceph-3-em-4-carboxylate, pentahydrate

Structural:



Pharmacological Category: Third generation cephalosporin antibiotic

Proposed Indication: Treatment of infections caused by a variety of susceptible micro-organisms, predominantly gram-negative, but also gram-positive micro-organisms and located at multiple anatomical sites.

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Dosage Form and Route of Administration: Sterile white or off-white dry-powder blend of two ingredients in vials and infusion bottles to be reconstituted for intravenous or intramuscular administration.

Ingredients

[redacted]

These 500 mg, 1.0 g, and 2.0 g vials, 1.0 g and 2.0 g infusion packs, and 6.0 g pharmacy bulk package containers have a carbon dioxide headspace. The sodium carbonate facilitates the dissolution of ceftazidime. When reconstituted with sterile water, the solution is clear.

Related Submissions:

Form 62-465 Ceftazidime (Glaxo)
IND 18,257 Ceftazidime (Glaxo), the companion IND

Microbiology and Manufacturing Controls: The reader is referred to the microbiological reviews by James R. King, Ph.D.

A letter from Glaxochem Limited to authorize FDA to refer to three Drug Master Files and a letter from Glaxo Operations UK Limited to authorize FDA to refer to one Drug Master File are submitted.

Ceftazidime is a semi-synthetic analogue of cephalosporin C. It is a bactericidal broad spectrum beta-lactamase-resistant cephalosporin that has unusual activity against gram-positive and gram-negative micro-organisms. It is active against certain species that have been resistant to other cephalosporins because of its beta-lactamase stability and it is particularly active against Pseudomonas aeruginosa and other Pseudomonas species. It is comparable to the activity normally associated with aminoglycosides.

MIC's were determined against approximately 950 strains for eight cephalosporins and gentamicin and are shown in the following table.

Table 19 The antibacterial activity of ceftazidime, eight other cephalosporins and gentamicin

Organism	(Number of strains)	Geometric mean MIC (ug/ml) at 10^5 cfu/ml									
		CAZ*	CTX*	MOX	CTZ	CMN	CPZ	CXM	CTM	CFS	GEN*
Ps. aeruginosa	71	1.3	15.7	15.1	31.6	28.2	6.4	432	167	3.7	12.5
Pseudomonas spp.	53	1.3	17.1	13.7	25.5	18.7	5.3	428	951	3.3	8.5
Proteus mirabilis	81	0.02	0.02	0.07	0.01	0.03	1.1	[illegible]	0.3	56.1	3.5
Indole +ve Proteus spp	91	0.07	0.06	0.1	0.08	0.08	3.2	[illegible]	8.0	71.4	6.8
E. coli	89	0.1	0.06	0.3	0.05	0.1	0.5	[illegible]	0.2	55.9	2.6
Klebsiella spp.	95	0.3	0.1	0.3	0.06	0.3	11.8	[illegible]	1.6	189	5.2
Enterobacter spp.	98	0.4	0.4	0.3	0.2	0.2	1.2	81.1	4.7	213	2.8
Citrobacter spp.	19	0.2	0.3	0.2	0.1	0.2	0.4	3.3	0.5	57.8	2.5
Serratia spp.	87	0.1	0.2	0.3	0.07	0.2	3.8	6.8	12.8	127	8.1
Salmonella/Shigella spp.	35	0.3	0.2	0.09	0.03	0.1	0.4	[illegible]	0.2	29.9	[illegible]
Haemophilus influenzae	42	0.1	0.01	0.1	0.02	0.02	0.07	2.1	1.0	88.3	0.8
Neisseria gonorrhoeae	16	0.04	0.006	0.04	0.02	0.02	0.02	[illegible]	0.02	3.5	0.3
Acinetobacter spp.	27	6.7	18.8	27.5	9.3	57.5	>200	122	131	135	48.6
Staphylococcus spp.	56	5.9	0.4	3.7	0.6	0.6	0.3	0.7	0.4	2.1	0.9
Meth-resistant Staph. spp.	19	35.7	26.3	30.3	185.0	11.9	15.8	9.6	7.4	9.3	0.4
Micrococcus spp.	5	7.6	0.8	16.0	2.6	2.6	2.3	1.8	0.8	9.2	0.06
Strept. pneumoniae	9	0.3	0.1	0.7	0.03	0.02	0.04	0.2	0.1	2.2	5.9
Strept. pyogenes	8	0.2	0.02	2.0	0.07	0.06	0.3	0.6	0.2	1.8	9.6
Streptococcus spp.	33	0.8	0.04	3.6	0.07	0.06	0.1	1.0	0.3	3.2	[illegible]
Strept. faecalis	5	32.4	1.3	125.0	125.0	35.8	8.0	34.1	64.6	125	17.9
Clostridium spp.	15	3.3	0.6	8.5	8.5	1.5	0.6	0.3	3.0	15.7	[illegible]
Cl. difficile	9	101.0	82.1	125.0	>500	62.0	53.1	20	>500	731	[illegible]
Bacteroides fragilis	24	8.9	8.2	0.6	3.8	7.7	16.8	[illegible]	52.5	26.9	[illegible]

* Additional strains of most species tested against these compounds

CAZ - Ceftazidime CTZ - Ceftizoxime CMZ - Cefmetazole GEN - Gentamicin
CTX - Cefotaxime CMN - Cefmenoxime CTM - Cefotiam
MOX - Moxalactam CPZ - Cefoperazone CFS - Cefsulodin (from pages 47-051 to 47-052)

Very high in vitro antimicrobial activity was found with the Enterobacteriaceae, Hemophilus, Neisseria, Streptococcus (except S. faecalis), and Pseudomonas species. Although the microbiological activity of ceftazidime against gram-positive and gram-negative organisms is similar to that of ceftizoxime and ceftriaxone, its activity against pseudomonads is said to be significantly higher. In most respects ceftazidime is similar to the activity of aminoglycosides. Poor activity against methicillin-resistant staphylococci and against Clostridium difficile was reported.

A summary of beta-lactamase stabilities of ten of the newer cephalosporins relative to the stability of cephaloridine is shown in the next table.

Table 29 Comparison of the relative rates of hydrolysis of ten cephalosporins by sixteen of the principal β-lactamases or representative β-lactamase types found in clinical populations

Name	β-lactamase Genetic origin	β-lactamase activity units/ml	Relative rates of hydrolysis									
			CER	CPZ	CPT	CFS	CMX	CTX	CTZ	CAZ	CMZ	MOX
TEM -1	R-plasmid	3.00	100	54	5	2	<1	<1	<1	0	<1	0
TEM -2	R-plasmid	1.99	100	61	7	3	1	0	1	0	1	0
SHV-1	R-plasmid	1.18	100	73	3	6	1	0	<1	0	0	0
OXA-1	R-plasmid	0.05	100	22	25	2	85	22	122	7	0	0
OXA-2	R-plasmid	0.06	100	80	NT	3	3	0	2	0	0	0
OXA-3	R-plasmid	0.15	100	47	NT	9	6	0	6	0	0	0
K1	Chromosomal: K.pneumoniae	1.86	100	3	22	4	7	7	<1	3	<1	<1
P99	Chromosomal: Ent.cloacae	2.50	100	1	7	<1	<1	3	<1	<1	<1	<1
2046E	Chromosomal,: Cit.intermedius b	4.07	100	32	38	8	8	15	1	<1	<1	<1
STH A	Chromosomal: Bact.fragilis	0.98	100	37	22	14	<1	0	1	1	0	<1
PSE-1	Pseudomonas specific R-plasmid	1.13	100	16	8	47	247	27	0	0	20	0
PSE-2	Pseudomonas specific R-plasmid	0.07	100	165	258	32	264	16	44	30	12	11
PSE-3	Pseudomonas specific R-plasmid	0.01	100	225	285	7	0	<1	36	8	0	8
PSE-4	Pseudomonas specific R-plasmid	2.46	100	4	2	0	3	1	0	2	0	0
S + A	Chromosomal: Ps.aeruginosa	0.16	100	0	14	15	0	15	1	<1	<1	0
PC-1	R-plasmid: Staph.aureus	0.01	100	62	0	38	39	0	0	30	0	0

N.T. = not tested
CER: cephaloridine, CPZ: cefoperazone, CPT: cefotiam, CFS: cefsulodin, CMX: cefmenoxime
CTX: cefotaxime, CTZ : ceftizoxime, CAZ: ceftazidime, CMZ: cefmetazole, MOX: moxalactam

Using the NCCLS method of disc testing and 30 mcg ceftazidime discs, the applicant proposes the following zone diameter breakpoints:

	MIC	Zone
Susceptible strains	Equal to or less than 16 mcg/ml	Greater than 18 mm
Intermediate strains	17-32 mcg/ml	15-17 mm
Resistant strains	Equal to or greater than 64 mcg/ml	Less than 14 mm

Cephalothin discs were unsuitable.

Animal pharmacology: The reader is referred to the pharmacology review by Gamil C. Debbas, Ph.D.

Following injection, ceftazidime is rapidly absorbed from muscle and subcutaneous tissues and peak blood levels are attained within 30 minutes. Except for cerebrospinal fluid and aqueous humor, ceftazidime diffuses well into tissues and extravascular fluids. Behavior, body temperature, and pupil diameter were not affected. Cardiovascular respiratory, and autonomic nervous system responses were normal. In the rat, ceftazidime crosses the placental barrier and is excreted by fetal kidneys.

In rodents the intramuscular injection of a 25% w/v solution was slightly irritating while intravenous injections were well tolerated. A 30% solution was well tolerated when instilled into the conjunctival sac. Dialysis fluid containing ceftazidime in a concentration of 0.15% w/v was not irritating upon intraperitoneal injection.

Ceftazidime may be up to 30% protein bound.

The primary route of excretion is in the kidney by glomerular filtration. There is no net tubular excretion and probenecid has no detectable effect on half-life. In the mouse renal tolerance was not affected by furosemide. In rats and dogs, doses ten times the clinical dose were well tolerated by the kidney. Larger doses were associated with increased urinary protein excretion, celluria, and the presence of enlarged phagosomes in renal tubules. No glomerular damage occurred at any dose level but renal tubular necrosis was seen in male rats given 90 times the clinical dose by subcutaneous injection.

Subcutaneous injections of 90 times the clinical dose daily for one month in female rats did not produce a rise in serum enzyme levels or histological evidence of liver damage. When treatment was extended to six months with the dose reduced to 30 times the clinical dose, increases in serum liver enzymes occurred and a number died with centrilobular liver cell necrosis. Doses up to ten times the clinical dose in dogs were not associated with a liver enzyme

increase.

The serum half-life is about 20 minutes in the mouse and is nearly one hour in the monkey. Traces reach the gastrointestinal tract through secretion through mucosa and from bile. Over 98% of ceftazidime is recovered, 95% from urine. There is no evidence of metabolism.

There is no effect on the central nervous system following subcutaneous doses of up to 40 times the normal maximum recommended daily dose of 90 mg/kg. There was no significant effect on blood pressure, heart rate, ECG and respiratory rate following intravenous doses up to three times the clinical dose.

Intracisternal doses larger than 1.25 mg/kg in rabbits caused hyperexcitability, sometimes leading to convulsions. In the rabbit a single 800 mg/kg dose, nine times the clinical dose in man, was without effect on renal function.

The applicant indicates that in the rat ceftazidime appeared to protect the animal from the nephrotoxicity of a ten-day course of gentamicin, amikacin, or tobramycin.

Doses of ten times the clinical dose and above in rats were associated with mild anemia. Local hemorrhage and hemosiderin-laden macrophages at the infection sites were thought to contribute to the anemia. Changes were reversible. There was no marrow depression, increased red cell fragility, or thrombocytopenia.

Ceftazidime lacks mutagenic potential.

In acute toxicity studies ceftazidime had a wide margin of safety. The LD_{50} values in mice, rats, dogs, and monkeys were greater than 5 g/kg after intravenous or subcutaneous dosing. Potential target organs that could be affected adversely at multiples of the expected human dose are the liver, kidney, and the hematopoietic system.

Clinical Pharmacology - Phase I Studies:

The reader is referred to the pharmacokinetic review dated March 15, 1984 by Vinod P. Shah, Ph.D.

Early pilot studies of ceftazidime were conducted with ceftazidime prepared from the acid by the addition of sodium bicarbonate in approximately equimolar ratios and made up to the appropriate volume. Doses were 125 mg to 750 mg IM and 125 mg to 500 mg IV and each dose/route was given to three volunteers. Injections were well tolerated and pharmacokinetic parameters for this preliminary sodium salt were calculated.

Investigators for pharmacokinetic studies at Glaxo were Stuart Murdoch Harding, M.D., B.S, B.SC., Head of the Department of Human Pharmacology,

Alexander James Munro, M.B.Ch.B., Assistant Pharmacologist, and George Robert Spencer, M.B.Ch.B., Assistant Pharmacologist in the Department of Human Pharmacology, Glaxo Group Research Limited, Greenford, Middlesex UB6 OHE England. The monitor was Roy Douglas Foord, M.D., D.T.M.& H., Medical Director of Glaxo Group Research, Limited.

In early Phase I studies of the final product, ceftazidime pentahydrate, subjects were healthy male volunteers from the Glaxo staff and ranged in age from 20 to 51 years. Each volunteer was given the protocol to read. Subjects who were allergic to antibiotics were excluded. Volunteers remained in the testing unit at Glaxo for at least two hours after dosing. Needles and tubing used for injections were kept patent with 100 iu heparin/ml of saline and volunteers were free to have lunch and return to their normal working routine in their own departments, returning only for blood sampling.

Doses, volumes, and routes of administration were as follows:

Dose/Route	IM	IV bolus	IV infusion
250 mg	-	10 ml	-
500 mg	2 ml	10 ml	20 ml
750 mg	3 ml	-	-
1 g	4 ml	10 ml	20 ml (10 ml*)
2 g	-	-	20 ml (10 ml*)

* Repeat dose study

Serum and urine specimens were analyzed by microbiological assay and sometimes also by HPLC. The computer program NONLIN was used to obtain pharmacokinetic parameters.

The essential findings of these pharmacokinetic studies are outlined below.

Intravenous Studies by Glaxo

1. Study No. HVT/79/26 Pharmacokinetics - two routes of administration. Single doses of 125 mg, 250 mg, 500 mg, and 750 mg of the monosodium salt, the zwitterionic form of ceftazidime, were given IM or IV to 23 volunteers. There was marked persistent pain and a rise in serum creatine kinase, an enzyme associated with muscle damage. Urine recovery was over 70%. Protein binding was less than 50%. The one and one-half hour half-life was considered to be long. There was no net renal tubular secretion. The zwitterionic form was not acceptable.

2. Study No. HVT/79/4 Pharmacokinetics - Uncontrolled. Single IV bolus doses of 250 mg of ceftazidime anhydrous betaine, as the sodium salt, were given to six volunteers. No adverse effects were noted. Serum levels were 20 mcg/ml at 5 minutes and were still above 1 mcg/ml at 6 hours. Urinary recovery was 43% in the first two hours and total recovery was 78%. Data fit a two-compartment model. The mean half-life was 1.8 hours. No metabolites were detected.

3. Study No. HVT/79/47 Pharmacokinetics - Controlled Single IV doses of 500 mg of ceftazidime anhydrous betaine as the sodium salt, alone and with a total of 1.0 g of probenecid (1.0 g followed by two 500 g divided doses) were given to four volunteers. Four additional volunteers received cefotaxime. No adverse effects were noted; however, there was a significant rise in serum creatinine (greater than 1.2 fold) after the second dose in three ceftazidime subjects and one cefotaxime subject. Values in two subjects were still abnormal on the fourth day after dosing. One subject subsequently received 30 one-gram IV doses over a ten-day period with no change in creatinine values. It was thought that these serum creatinine elevations were solely due to factors associated with the assay.

One subject had an elevated creatine kinase and aspartate transaminase on the day after the second dosing. He cycled to work.

Serum levels were about 45 mcg/ml at 5 minutes and were 1.3 mcg/ml at 8 hours. Urinary recovery was 55% of the dose in the first two hours and 86% in 24 hours. Probenecid did not affect serum levels or urinary recovery. Half-life was 1.9 hours. Cefotaxime was metabolized to desacetyl cefotaxime. It had a shorter half-life because of renal tubular excretion and metabolism of the antibiotic.

4. Study No. HVT/79/48 Pharmacokinetics - controlled. Single IV bolus doses of one gram of ceftazidime anhydrous betaine as the sodium salt alone and with two grams of probenecid (one gram followed by two 500 mg doses) were given to four volunteers in a crossover design. Four other volunteers received one gram of cefotaxime as the sodium salt and ceftazidime in a crossover design. One volunteer experienced itching of eyes, irritation and tightening of the throat and a feeling of warmth after ceftazidime.

The mean serum level was 87.4 mcg/ml at 5 minutes, 37 mcg/ml at one hour, 10 mcg/ml at 4 hours, and 3.6 mcg/ml at 8 hours. Just over 50% of the dose was excreted within the first two hours and 85% within 24 hours. Probenecid did not affect serum levels or urinary recovery. Cefotaxime was metabolized to desacetyl cefotaxime. Conversion was rapid with the highest serum levels, 12 mcg/ml, at 5 minutes. Ceftazidime data fit a two-compartment model. The mean half-life was 1.8 hours. The AUC was twice that following a 500 mg dose.

5. Study No HVT/81/4, 9, 10 Tissue penetration - Uncontrolled. Single intravenous doses of one gram of ceftazidime anhydrous betaine (as the sodium salt) were given to eight volunteers in three studies to study tissue penetration using adherence to cotton thread, suction, and cantharides blister techniques. There was some residual pigmentation at the sites of the cantharidin-induced blisters and suction blisters for some months. One suoject developed cellulitis. Absorption-excretion data were similar to that reported above.

Two different rates of absorption and elimination indicate two types of kinetic behavior.

Rapidly equilibrating compartment - cotton threads in the proximity of the capillary bed. The mean peak level was 26.7 mcg/ml and peaks occurred between 20-60 minutes.

Slowly equilbrating compartment - Cantharidin-induced blister and suction blisters further away from the capillary bed. The mean peak level in the cantharidin-induced blister was 24.2 mcg/ml. Peaks occurred 20-240 minutes after dosing. The mean peak level in suction blisters was 31.3 mcg/ml and peaks occurred between 40 and 240 minutes after dosing.

Many factors must be considered in the measurement of tissue penetration and the levels achieved depend upon the characteristics of the specific tissue being studied. Beyond the first two and one half hours, ceftazidime levels in the two types of blisters exceeded serum levels.

6 A. Study No. HVT/80/2 Pharmacokinetics - Uncontrolled two-part study. Single IV infusions of 500 mg of ceftazidime over 30-minute periods were given to six volunteers. After 500 mg, the mean serum level was 41.5 mcg/ml at 30 minutes and pharmacokinetic parameters were similar to those found after a bolus injection of the same dose.

6 B. Study No. HVT/80/2 Pharmacokinetics - Uncontrolled Single IV infusions of one gram of ceftazidime over 20-minute periods were given to seven volunteers. The mean serum level at the end of the infusion was 68.9 mcg/ml and levels around 3 mcg/ml were present at 8 hours. Urinary excretion measured 52% of the dose in the first two hours and 84% in 24 hours. All but 3% was recovered in the first 8 hours.

7. Study No. HVT/80/7 Pharmacokinetics - Uncontrolled Single 20-minute IV infusions of two grams of ceftazidime anhydrous betaine as the sodium salt were given to seven volunteers. No adverse reactions occurred. The mean serum level at the end of the infusion was 169.6 mcg/ml. At 6 hours the mean serum level was 10.4 mcg/ml and was 2.4 mcg/ml at 10 hours. The mean urinary excretion was 55% of the dose in the first two hours and 87% in 24 hours. Half-life was 1.9 hours. The AUC was 266 mcg/ml/hr., 1.86 times the AUC for the one gram dose.

Intramuscular Studies by Glaxo

8. Study No. HVT/79/46 Pharmacokinetics - Uncontrolled Single IM injections of 500 mg of ceftazidime anhydrous betaine, as the sodium salt, were given to eight volunteers. No adverse reactions occurred. The mean peak serum level was 17.4 mcg/ml and was attained at one hour. The mean serum level was 8.4 mcg/ml at 4 hours and 2.3 mcg/ml at 8 hours. Urine recovery was 80% of the dose in the first 8 hours and 85% in 24 hours. The data fit a one-compartment model. Half-life was 2.2 hours. As with all of the ceftazidime studies, no metabolite was detected.

9. Studies HVT/80/6 and HVT/80/22 Tissue Penetration - Uncontrolled Single intramuscular doses of 750 grams of ceftazidime anhydrous betaine (as the sodium salt) were given to seven volunteers in studies of tissue penetration using adherence to cotton thread and suction blisters. The three thread subjects were mobile and two of the four blister subjects were recumbent for 2-3 minutes after dosing. No local or general adverse effects

occurred. There was residual pigmentation from the suction blisters for some months after the procedure.

Mean peak serum levels in the mobile and recumbent subjects were considerably different, and were 36.4 mcg/ml and 20.8 mcg/ml, respectively. Peak levels of 15.7 mcg and 17.9 mcg/ml were achieved in the fluid adherent to the cotton threads. Peak suction blister levels were 12.6 and 20.8 mcg/ml at 2 and 3 hours, respectively.

10. Study No. HVT/80/8 Pharmacokinetics - Crossover controlled Single IM injections of one gram of ceftazidime anhydrous betaine, as the sodium salt, and cefotaxime were given to eight volunteers. No local or general adverse reactions were noted. Both injections were painful. Pain was more pronounced with cefotaxime.

The mean ceftazidime peak serum level was 40.2 mcg/ml at one and one-quarter hours after dosing. Mean serum levels were 9.6 mcg/ml at six hours and 5.4. mcg/ml at 8 hours. Urinary excretion was 78.9% of the dose in the first 24-hour period, all but 5.2% being recovered in the first 8 hours. No metabolites were detected. Data fitted a one-compartment model. The mean serum half-life was 2.0 hours.

The mean cefotaxime peak serum concentration was 36.7 mcg/ml at about one hour. The mean serum level was 1.5 mcg/ml at 6 hours and equal to or less than 1.0 mcg/ml at 8 hours (detectable in only one subject). Total urinary excretion of drug plus its desacetyl metabolite was 83.8% over 24 hours. Data fitted a one-compartment model but because of early peak values, the absorption phase could not always be well-delineated. Half-life ranged from 0.4 to 1.8 hours.

11. Study No. HVT/80/16 Pharmacokinetics - Uncontrolled Single IM injections of one gram of ceftazidime anhydrous betaine, as the sodium salt, in aqueous solution with 1% lignocaine were given to six volunteers. Pain was very slight and transient. The mean peak serum level was 43.9 mcg/ml and urinary excretion averaged 97.9% of the dose.

Other Glaxo Studies

12. Study No. HVT/80/11 Pharmacokinetics - Uncontrolled Single oral doses of 250 mg of ceftazidime anhydrous betaine as the sodium salt were given to seven volunteers. The mean urinary concentration was 1.5 mcg/ml and the mean twelve-hour urinary recovery was less than 1% of the dose. The applicant concludes that the sodium salt of ceftazidime is not absorbed when taken orally.

13. Study No. HVT/80/10 Cardiovascular and subjective effects - Randomized crossover Single two-gram, 20-minute intravenous infusions of ceftazidime and single infusions of water soluble vitamins as placebo were given to six volunteers in a randomized, double-blind crossover design. There were no changes in systolic or diastolic blood pressure or heart rate. ECG recordings were unaffected.

14. Study No HVT/80/9 Multiple-dose pharmacokinetics - Uncontrolled. Ten-day courses of one gram of ceftazidime anhydrous, as the sodium salt, three times daily were given intramuscularly to six volunteers and intravenously to another six volunteers. The diluent for three subjects in each group contained 1% lignocaine. Creatinine kinase was elevated in two subjects that received intramuscular doses. Mean peak serum levels after the first and 25th intramuscular doses were 47.5 mcg/ml. Peaks occurred between 40 minutes and two hours after dosing. The AUC after the first dose was 175 mcg/ml and was 186 mcg/ml after the 25th dose. There was no accumulation. The use of 1% lignocaine considerably reduced pain on injection.

The mean peak serum level after the first intravenous dose was 86.6 mcg/ml. The mean trough level was 7.5 mcg/ml.

15. Study No. HVT/80/26 Multiple-dose Pharmacokinetics - Uncontrolled Ten-day courses of two-gram bolus injections of ceftazidime three times daily were given intravenously to eight volunteers. One volunteer withdrew because of an urticarial rash. No drug accumulation occurred. Serum levels and urinary recoveries after the first dose were similar to those after the 28th dose.

Summary of Glaxo Studies:

Ceftazidime has acceptable pharmacokinetic properties after parenteral administration. It is metabolically stable and has a longer serum half-life than other beta-lactam antibiotics with a similar degree of protein binding. It is eliminated solely by renal glomerular filtration.

Ceftazidime is well-tolerated both locally and systemically, and its kinetics are practically unaltered by lignocaine (lidocaine) if it is necessary to give IM injections with an anesthetic agent.

A 500 mg IV or IM dose given two or three times a day may be recommended for susceptible enterobacteria causing uncomplicated infections or for urinary tract infections. The one-gram IM dose may be recommended for the treatment of systemic infections caused by most bacterial organisms. For the treatment of systemic infections due to Staphylococcus aureus, P. aeruginosa and Acinetobacter species, especially when tissue penetration may be impaired, a one-gram IV injection, preferably three times a day, is suggested. The two-gram IV injection should be needed only in a life threatening situation.

As with other drugs of this class, reductions in dosage or in dosage frequency should be made in renal impairment. It is suggested that caution be exercised in patients whose glomerular filtration rate is below 50 ml/min.

Other Foreign Studies (not Glaxo)

16. Pharmacokinetic and Safety Data from Healthy Volunteers These were university and hospital studies conducted to confirm and extend Glaxo's data.

a) Armstrong GC, et al. Comparison of ceftazidime and cefamandole pharmacokinetics and blister fluid concentrations. Antimicrob Agents and

Chemother 1981 Sept; 20 (3): 356-358.

b) Ruscl L, et al. Comparative multiple-dose pharmacokinetics of cefotexime, moxalactam, and ceftazidime. Antimicrob Agents and Chemother 1981 Nov; 20 (5): 567-575.

c) Tjandramaga TB, et al. Comparative pharmacokinetics of ceftazidime and moxalactam. Antimicrob Agents and Chemother 1982; 22 (2): 237-241.

d) Sommers DK, et al. The pharmacokinetics of ceftazidime in male and female volunteers. (An unpublished report signed Jan. 18, 1983.)

e) Loce H.. Specialist opinion on pharmacokinetics of ceftazidime (GR20263) for application for license by Glaxo Research Ltd. Berlin University, Berlin, Germany. July 15, 1981.

f) Mondorf AW, et al. Assessment of nephrotoxic potential of ceftazidime and ceftazidime/tobramycin combinations in volunteers. Infection 1983: II Suppl 1: S57-S62.

In these six reports, 64 volunteers received 308 doses of ceftazidime. Sixteen female volunteers were included. These studies confirm the reports from Glaxo. The only major difference was in cantharidin blister fluid levels, Glaxo's levels being lower. Differences in methodology (blister size) were thought to be responsible. Two cases of diarrhea were reported by Mondorf. Pain on intramuscular injection was noted by Tjandramaga and Sommers.

17. Pharmacokinetic Data from Special Populations

a) Study No. CAZ/KIN/OP/12.01 Prinsloo, J. G., Head of the Department of Pediatrics at Kalafong Hospital in Pretoria, South Africa, studied the pharmacokinetics of ceftazidime in 53 neonates and infants up to the age of one year. They were receiving treatment for a variety of infections and were given ceftazidime in single intravenous doses of 30 mg/kg (range 25.0 to 35.7 mg/kg). There was considerable interpatient variability in serum levels in patients below two months of age where the mean serum level at 3 hours was 54.1 mcg/ml. This level declined to 18.6 mcg/ml at 9 hours. The mean serum half-life was 4.18 hours. Values for older infants were similar to those of adults. The investigator recommends doses of 30 mg/kg/day for infants less than two months of age and doses of 30 mg/kg twice a day for infants 2 to 12 month of age. Until more experience is gained trough levels should be monitored.

b) Jackson MA, Kusmiesz H, Nelson JD. Ceftazidime pharmacokinetics in pediatric patients. 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy 1982 Oct; Poster No 805, Miami, Florida. Single 15-minute intravenous infusions were given to 25 pediatric patients ranging in age from 5 weeks to 11 years at the University of Texas Southwestern Medical School in Dallas.

No. pts	Dose mg/kg	Peak Conc. mcg/ml	T 1/2 alpha hrs.	T 1/2 beta hrs.	VD l/kg	Clearance ml/min/kg
Gram-Neg Infections						
8	15	37.8	0.58	1.65	0.73	5.03
5	50	186.4	0.22	1.72	0.52	3.75
Cystic Fibrosis						
6	50	150.8	0.21	1.35	0.63	5.44
6	75	175.5	0.24	1.24	0.85	7.28

Investigators conclude that a dosage of 50 mg/kg appears to be adequate for infections caused by S. aureus, P. aeruginosa, and a variety of enterobacteria and that 75 mg/kg may be necessary in cystic fibrosis patients.

Reviewer's Comment: This study is from Dallas, Texas, yet it is classified by the applicant under foreign studies.

c) Blumer JL. et al. Ceftazidime in cystic fibrosis: pharmacokinetics and therapeutic response. 1982 ICAAC Abstract. After single intravenous doses of 50 mg/kg in 20 adult cystic fibrosis patients, T 1/2 alpha was 0.28 hours and T 1/2 beta was 1.59 hours. Probenecid was without effect.

d) Giamarellou H. et al. A study of cefoxitin, moxalactam, and ceftazidime in kinetics in pregnancy. (Report presented July 1982 at the University of Sussex.) Labor was induced in nine women at 20 weeks gestation (mean). Ceftazidime amniotic fluid levels were between 1 and 5 mcg/ml.

19. Pharmacokinetics in Patients with Impaired Renal Function

a) Gower PE, et al. Kinetics of ceftazidime in renal impairment. Current Chemotherapy and Immunology Prac. 12th Intern Congress of Chemotherapy 1982; 1: 498-499.

b) Norrby, SR, et al. Ceftazidime's pharmacokinetics in patients and effects on the renal function. Jo of Antimicrob Chemother 1982; 10: 199-206.

c) Hoeffler D, et al. The pharmacokinetics of ceftazidime in normal and impaired renal function (Abstract).

d) Ober B, et al. Pharmacokinetics of ceftazidime in uremic patients. 22nd ICAAC 1982. Abstract No. 806.

e) Strough AB, et al 22nd ICAAC 1982. Abstract No. 801.

In these studies, 23 health volunteers and 67 patients with varying degrees of impairment of renal function, 17 of whom were on intermittent dialysis, were studied. Results show that the half-life of ceftazidime increased with worsening renal function. The volume of distribution was unaffected by the degree of renal impairment and clearance was directly related to the serum elimination rate constant and the glomerular filtration rate. The mean half-life of ceftazidime increased from 1.8 hours when renal function was normal to 24 hours when glomerular filtration was absent.

Suggested posology:

Creatinine Clearance (ml/min)	Approx. serum creatinine (mc mol/l)	Unit dose of ceftazidime (g)	Frequency (hours)
50-31	150-200	1.0	12
30-16	200-350	1.0	24
15-6	350-500	0.5	24
Under 5	Over 500	0.5	48

The usual daily dose for adults with normal renal function is 3 to 4 grams given either as one gram every 8 hours or two grams every twelve hours. A dose of 6 grams may be given to immunocompromised patients or when the severity of the infection suggests a need for higher doses. In similar patients with renal insufficiency, the unit dose of ceftazidime in the posology table may be increased 50% or the dosing frequency increased appropriately. Trough serum levels of ceftazidime should not exceed 40 mcg/ml.

Ceftazidime is removed by haemodialysis, therefore, dosing at the end of dialysis is recommended.

19. Levels in Tissues and Fluid Obtained from Patients in Surgical Units.

Nine studies of ceftazidime levels in tissues and fluids from 174 patients in surgical units were reported. Most patients received single two-gram intravenous doses. Some patients received single or repeat one-gram intramuscular doses.

After single 2-gram IV doses

Mean peak organic bone levels	12 pts.	31.1 mcg/g
whole bone levels	29 pts.	17.0 mcg/g
Mean peak peritoneal fluid level	31 pts.	66.7 mcg/ml at 7.5 min.
peritoneal drain fluid	9 pts.	25.6 mcg/ml at 2 hrs.
Mean peak myometrial level	30 pts.	18.1 mcg/ml in 2 hrs.
endometrial level	30 pts.	18.9 mcg/ml in 2 hrs.
salpingeal level	30 pts.	18.7 mcg/ml in 2 hrs.
Mean heart muscle level	29 pts.	11.5 mcg/ml
Mean skeletal muscle level	29 pts.	8.8 mcg/ml
Mean skin level	29 pts.	11.0 mcg/ml

Mean fat level	29 pts.	10.2 mcg/ml
Mean peak fluid level from periprosthetic space after hip replacement	12 pts.	25.6 mcg/ml at 2 hrs.
Aqueous humor	ng	11.1 mcg/ml

After one gram IM

Mean amniotic fluid level	9 pts.	1.0-5.5 mcg/ml
Aqueous humor	ng	2.3 mcg/ml

20. Levels in Body Fluids from Patients in Medical Units

Six studies of the penetration of ceftazidime from 128 patients on medical units were reported.

Sputum

1 g dose IM	47 pts.	Pneumonia or Chronic bronchitis	3.2 mcg/ml (2-4 hr. collection) 3.0 mcg/ml (4-6 hr. collection) 2.2 mcg/ml (6-8 hr. collection)
2 g dose IM	18 pts.	Pneumonia or Chronic bronchitis	2.4 mcg/ml (2-4 hr. collection) 3.2 mcg/ml (4-6 hr. collection) 2.5 mcg/ml (6-8 hr. collection)
50 mg/kg IV	6 pts. 15 pts.	Cystic fibrosis Cystic fibrosis	Under 1 to 8 mcg/ml (one study) 4-15 mcg/ml (second study)

Cerebrospinal fluid

Four 2 g doses IV	12 pts.	Bacterial meningitis	12.7 mcg/ml at 2 hours.
One 2 g dose IV	10 pts.	Normal meninges	0.1 to 0.8 mcg/ml
(ng)	3 pts.	Ventricular shunts	Low

Pleural fluid

Single 2 g	3 pts.	Bronchial carcinoma	30 mcg/ml at 4 hours 12 to 35 mcg/ml up to 4 hours after dosing

Pharmacokinetic Studies in United States

21. Study No. CAZ-K01 Gerald P. Body, M.D., Medical Director of the Clinical Research Center (M.D. Anderson Hospital) at the Un. of Texas Systems Cancer Center, Texas Medical School, Houston, Texas, measured ceftazidime pharmacokinetic parameters in 42 hospitalized adult patients with malignant diseases after single and multiple intravenous doses. Non-neutropenic patients received 1.0 or 2.0 grams as a single dose or multiple dose every 8 hours. Neutropenic patients received 1.0-gram infusions over 2-hour periods every four hours.

	No. pts.	Mean T 1/2 (hrs)	AUC (mg/h/L)	Total Body Clearance (ml/min)	VD (l/kg)	Mean Peak Conc. (mcg/ml)
Single Dose						
1.0 g	11	1.91	147.0	126.8	0.26	70
2.0 g	11	1.77	239.0	141.3	0.30	118
Multiple Dose	10	1.7	243.2	145.2	0.29	

Accumulation was said to be minimal and peak and trough levels after the fourth and fifth doses were essentially the same as those after the first dose.

22. Study No. CAZ-K03 Judith Lois Axelrod, M.D., Chief of the Infectious Disease Section, St. Luke's Roosevelt Hospital, New York, New York, conducted an uncontrolled study of ceftazidime concentrations in aqueous humor after the intravenous administration of two grams to 24 patients just before elective cataract extractions. The mean age was 70 years and patients ranged in age from 32 to 84 years. No adverse reactions were noted.

Peak aqueous humor concentrations occurred between 30 minutes and two hours. Mean concentrations in serum and aqueous humor are shown below:

	Mean Concentrations (mcg/ml)				
	30 min	1 hr	2 hr	4 hr	6 hr
Aqueous humor	2.8	4.0	3.2	3.4	1.9
Serum	123	78	76	22	14.6

Elimination from the aqueous humor compartment is much slower than elimination from the central compartment. The calculated elimination half-life was 6.3 hours compared with a serum half-life of 1.9 hours. Aqueous humor ceftazidime levels were well above the MIC_{90} for E. coli, klebsiella species, Proteus mirabilis, indole-positive Proteus species, and Pseudomonas aeruginosa.

23. Study No. CAZ-K05 Jeffrey L. Blumer, Ph.D., M.D., Pediatric Pharmacology Division, Rainbow Babies and Childrens Hospital, Cleveland, Ohio,

conducted an uncontrolled, single-dose, pharmacokinetic study of 50 mg/kg ceftazidime doses in 27 patients who were over five years of age and who were diagnosed as having cystic fibrosis. Six patients received probenecid with the ceftazidime in a second dosing.

The pharmacokinetic characteristics best fit a two-compartment open model. Without probenecid, the mean half-life was 1.48 hours and the mean clearance was 137.6 ml min/1.73 m^2. The mean peak serum concentration was 250 mcg/ml. Urinary excretion was 61% of the dose in two hours and 83% in eight hours. Probenecid did not significantly alter the parameters.

One patient reported nausea, emesis, and facial erythema. An urticarial wheal and rash were noted at the injection site. The patient had a history of penicillin allergy.

The applicant concluded that pharmacokinetic parameters are not altered in fibrocystic patients.

24. Study No. CAZ-K06 George L. Drusano, M.D., University of Maryland School of Medicine, Division of Infectious Disease, Baltimore Veterans Administration Hospital, Baltimore, Maryland, conducted a controlled trial to compare the pharmacokinetic parameters of ceftazidime and moxalactam and to compare the duration of acceptable antimicrobial activities for specific species. Six healthy adult male volunteers received 2000 mg of each antibiotic intravenously over a 30-minute period in a crossover design with a one-week washout period. No adverse experiences were reported.

	Ceftazidime	Moxalactam
Serum Concentrations		
Immediately after dosing	159 mcg/ml	220 mcg/ml
At 8 hours	3.7 mcg/ml	13.4 mcg/ml
Half-life	1.75 hrs.	2.5 hrs.
Volume of Distribution	0.21 l/kg	0.17 l/kg
Urinary Excretion at 6 hrs	70% of dose	70 % of dose

The MIC_{90}'s for both antibiotics were generally under 1.0 mcg/ml for 12 and 17 major species (577 strains) that were tested. The MIC_{90} for ceftazidime was 8.0 mcg/ml for Enterobacter hafnia, Pseudomonas aeruginosa, and Staphylococcus aureus. The MIC_{90} for moxalactam was 32 mcg/ml for Enterobacter hafnia, and 128 mcg/ml for Pseudomonas aeruginosa.

Consistently high serum bactericidal activities were found. Concentrations of both antibiotics were still present in the serum eight hours after dosing and were adequate to inhibit most Enterobacteriaceae. Only ceftazidime levels were adequate to inhibit Pseudomonas aeruginosa six hours after dosing.

25. Study No. CAZ-K04 William Lance George, M.D., UCLA Center for the Health Sciences, V.A. Wadsworth Medical Center, Los Angeles, California, conducted a pharmacokinetic study of single one-gram intravenous doses of

ceftazidime in 18 adult patients with either normal or impaired renal function. Subjects were grouped according to the degree of renal impairment.

Sergio Acchiardo, M.D., Memphis Tennessee, conducted the same study using the same protocol with 26 subjects. Results are shown below.

No.	Normalized Creatinine Cl. (ml/min/1.73 M^2)	Half-life (hrs.)	Normalized Total Body Clearance (ml/min/1.73 M^2)	VD (l/kg)
Dr. George				
6	119 ± 10	1.7 ± 0.1	106 ± 5	0.19 ± 0.01
1	39	8.5	28	0.25
2	23 ± 3	13.0 ± 4.8	21 ± 6	0.30 ± 0.02
3	10 ± 2	21.3 ± 4.4	10 ± 1	0.25 ± 0.04
6	0	30.8 ± 2.4	7 ± 1	0.24 ± 0.02
Dr. Acchiardo				
8	111.1 ± 8	2.1 ± 0.34	115 ± 16	0.225 ± 0.01
3	45.9 ± 5.5	4.7 ± 0.85	32.3 ± 5.1	0.165 ± 0.007
3	19.8 ± 1.7	11.3 ± 2.9	19.1 ± 3.1	0.215 ± 0.028
6	12.9 ± 1.0	15.4 ± 2.7	11.7 ± 1.1	0.210 ± 0.025
6	0	32.2 ± 2.2	4.9 ± 0.6	0.212 ± 0.026

No adverse experiences were reported.

Data obtained in these studies may be used to predict serum concentrations in the presence of renal insufficiency. The following dosage adjustments are recommended:

Creatinine Clearance (ml/min)	Dosage
Over 50	Normal dose and schedule
31-50	1000 mg every 12 hours
16-30	1000 mg every 24 hours
6-15	500 mg every 24 hours
Under 6	500 mg every 48 hours
Dialysis	1000 mg after each dialysis

26. Study No. CAZ-K15 Alfred P. Kraus, Jr., M.D., Chronic Ambulatory Peritoneal Dialysis, Division of Nephrology, Department of Medicine, University of Tennessee, Memphis Tennessee, measured the pharmacokinetic characteristics of ceftazidime during intermittent peritoneal dialysis and continuous ambulatory peritoneal dialysis in six patients with end-stage renal disease receiving maintenance peritoneal dialysis. Each patient had four dialysis exchanges over a period of 12.5 hours. Immediately after the first dialysate was instilled, a single 1.0 gram dose of ceftazidime was given intravenously.

Results show that the maximum amount of ceftazidime removed during a single exchange is 7% at a dwell time of 7.4 hours or longer and the rate of removal up to 7.4 hours is inversely related to time. The number of exchanges over a 24-hour period has little effect on the overall elimination of ceftazidime. Half-life is 22-24 hours. For patients receiving intermittent peritoneal dialysis or chronic ambulatory peritoneal dialysis, an initial dose of 1.0 g followed by 0.5 g every 24 hours would result in approximate peak and trough concentrations between 80 and 20 mcg/ml.

27. Study No. CAZ-K10 Jorge O. Blanco, M.D., University of Texas Health Science Center, San Antonio, Texas, measured ceftazidime concentrations in human breast milk following intravenous therapy. Eleven post-partum women received 2.0 g q 8 h. Ceftazidime was excreted in breast milk. One hour after the fifth to seventh dose the mean concentration was 4.1 mcg/ml. Concentrations 24 hours later in two patients show that there was no accumulation.

28. Study No. CAZ-K12 Thomas Roger Beam, M.D., Chief, Infectious Disease Section, Buffalo V.A. Medical Center, Buffalo, New York, studied pharmacokinetics in ten adult male volunteers with impaired hepatic function. Volunteers, patients with alcoholism and other disorders from the clinic population of the Division of Gastroenterology, received 2.0 g of ceftazidime intravenously every 8 hours for four days. Changes from baseline laboratory values were measued. No adverse experiences were noted.

Insufficient data were available to analyze pharmacokinetics accurately. This study is continuing. No changes in hepatic enzymes were observed. One patient experienced a transient rise in total bilirubin.

29. Study No. CAZ-K02 John D. Nelson, M.d., Professor of Pediatrics, Un. of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas, measured single-dose pharmacokinetic parameters in 33 hospitalized children 11 years of age and under, with and without a complication of cystic fibrosis. This study is similar to Study No. 17b, above.

Based upon the results of this study, a ceftazidime dose of 25 to 50 mg/kg up to a maximum of 2 grams q 8 h administered to children one month of age and older will most likely provide serum concentrations within the therapeutic range for susceptible pathogens during most of the dosing interval. A dosing adjustment is not required for children as young as one month. In the fibrocystic patient, a dose of 50 mg/kg every 8 hours may be effective; however, a dose as high as 75 mg/kg every 8 hours may be required to treat

patients with pulmonary infections because of the intractable nature of these infections.

30. Study No. CAZ-K18 John D. Nelson, M.D., above, conducted a multiple-dose study of ceftazidime pharmacokinetics in pediatric patients. Ten patients between one month and eleven years of age were enrolled. The mean age was 2.9 yrs in the non-fibrocystic group and 4.9 yrs in the fibrocystic group. Five patients without cystic fibrosis received 50 mg/kg intravenously every 8 hours and the five fibrocystic patients received 75 mg/kg every 8 hours for 2 or 3 days. Each dose was infused over a 15-minute period. No adverse reactions were noted.

Unfortunately, the collection of serum samples beyond 6 hours after dosing was not done, consequently calculations are only approximations. Accumulation does not occur at the doses used. Results were consistent with those from single doses. Patients with cystic fibrosis exhibited slightly larger volumes of distribution, somewhat greater clearance rates, and marginally shorter half-lives.

31. Study No. CAZ-K17 W. Manford Gooch III, M.D., Primary Children's Medical Center, Department of Pathology, Salt Lake City, Utah, studied pharmacokinetic parameters in neonates between one and nine days of age. Eleven patients from Latter Day Saints Hospital or Primary Children's Hospital received single intravenous infusions of 30 mg/kg. The mean age was 3.7 days. Data from ten patients were analyzed.

The mean peak concentration was 96.5 mcg/ml. The mean terminal half-life was 4.7 hrs., the mean VD was 0.6 l/kg. In neonates renal excretion mechanisms have not completely matured and the elimination of ceftazidime may be prolonged relative to the rates observed in older children and adults. A 30-mg/kg dose given every twelve hours can be expected to produce therapeutic concentrations over a 12-hour dosing interval.

Clinical Efficacy Studies:

Similar protocols and case report forms were used in each of the countries where ceftazidime was evaluated. Efficacy data in the application were obtained primarily from patients in United States. Data from Canada, Europe, and the United Kingdom were also included. Included in this application as primary data are 464 case reports from studies sponsored by Glaxo Group Research in England.

Patients enrolled in the ceftazidime clinical trials had a pretreatment battery of laboratory tests performed to establish baseline values. Most patients were tested at least once during therapy and again at the completion of therapy. Every value that was outside the range of normal for the testing laboratory was categorized on a nine-point scale (See pages 11-004 to 11-005).

Note: In response to the medical officer's request, summary efficacy tables in the original submission were revised in the amendment dated Sept. 5, 1984 to disqualify cases for which there was no susceptibility test report.

Controlled Clinical Trials - Dose Ranging Studies

1. Acute Lower Respiratory Tract Infections

a) Study No. CAZ-R01 A randomized controlled clinical trial comparing two doses of ceftazidime in the treatment of acute lower respiratory tract infections and bacteremia was conducted at five clinical centers. Hospitalized adult patients received either 0.5 gram or 1.0 gram of ceftazidime intravenously every eight hours for 5-10 days. Patients were diagnosed as having pneumonia, bronchitis, pneumonitis, or an unspecified LR.

Positive pretreatment cultures of bronchopulmonary secretions obtained within 48 hours of the start of treatment and pretreatment chest X-rays were required for LRI. At least two pretreatment blood cultures were required to confirm a presumptive diagnosis of bacteremia based upon symptoms in these patients. Isolated organisms must be susceptible to ceftazidime. Symptoms were temperature change of greater than 2°F, toxic clinical appearance, sudden onset of gastrointestinal symptoms, change in cerebral function, tachycardia, and respiratory alkalosis. Cultures and susceptibility tests were repeated between 24 and 48 hours after treatment was discontinued.

Hypersensitive patients, pregnant and lactating patients, patients with renal or hepatic dysfunction or neutropenia, and patients on other antimicrobial agents were excluded. Exclusions were repeated in most subsequent protocols.

Diagnoses were pneumonia - 153 patients, empyema - one patient, bronchitis - 20 patients, and pneumonitis - twice. It was not given for one patient.

Investigators were

Thomas M. Nolen, M.D., Columbiana Clinic, Columbiana, Alabama,
Stephen F. Zellner, M.D., Fort Myers, Florida,
Rodney M. Snow, M.D., Norwood Clinic, Birmingham, Alabama,
Lawrence J. Eron, M.D., Fairfax, Virginia, and
Dieter W. Gump, M.D., Un. of Vermont Dept. of Med., Burlington, Vermont.

Lower Respiratory Tract Infections (R01)

	Nolen		Zellner		Snow		Eron		Gump	
	0.5g	1.0 g	0.5g	1.0g	0.5g	1.0 g	0.5g	1.0g	0.5g	1.0g
No. Patients	51	49	26	28	18	18	1	4	2	2
% with other Disorders										
Cardiovasc.	33.3%	24.5%	42.3%	32.1%	66.7%	61.1%	-	50%	-	-
Pulmonary	54.9%	57.1%	30.8%	21.4%	44.4%	11.1%	1/1	25%	-	-
Age (yrs)										
Under 18	-	-	1	-	-	-	-	2	-	-
18-25	2	1	2	2	2	-	1	2	-	-
26-35	3	1	-	-	-	-	-	-	-	-
36-50	8	9	1	4	1	4	-	1	-	1
51-65	12	14	3	7	3	3	-	-	-	-
Over 65	26	24	19	15	12	11	-	1	2	1
Mean (yrs)	61.3	62.5	66.3	62.9	65.0	68.2	21.5	41.5	77.5	56.5
Sex M	29	24	13	20	12	10	0	2	0	2
F	22	25	13	8	6	8	1	2	2	0
Mean Duration (Days)	5.9	5.7	8.6	8.4	7.7	8.4	9.5	9.0	9.5	6.0

S. pneumoniae septicemia was diagnosed in two of Dr. Snow's patients who were treated with 0.5 gram of ceftazidime. Both were qualified and both organisms were eradicated (Volume 11, page 211).

Lower Respiratory Tract Infections - Outcome

	Nolen		Zellner		Snow		Eron		Gump		Total	
	0.5g	1.0g	0.5g	1.0g	0.5g	1.0g	0.5g	1.0g	0.5g	1.0g	0.5g	1.0g
Clinical Response												
(Evaluable pts.)												
No. cured	38	35	6	5	11	12	2	2	1	0	58	54
% cured	79.2%	76.1%	35.3%	29.4%	68.8%	85.7%	0	0	0	0	69%	66%
No. Improved	10	10	9	8	5	2			0	0	24	20
No. Failures	0	1	2	4	0	0	0	2	0	0	2	7
Bacteriological Response												
(No. Eradicated/ No Qual Isolates)												
E. coli	10/10	7/7			2/2						12/12	7/7
Klebsiella	7/8	5/5	1/1	4/4	2/2						10/11	9/9
P. mirabilis	1/1	4/4	2/2		1/1			1/1			4/4	5/5
Proteus, indole +		1/1										1/1
Enterobacter	5/5	7/7	3/3		0/1			0/1			8/9	7/8
Citrobacter		2/2			1/1						1/1	2/2
Serratia						2/2						2/2
Hemophilus			1/1			1/1					1/1	1/1
H. influenzae												
Acinetobacter						1/1						1/1
P. aeruginosa	6/6	2/2	1/1		2/3	1/1	0/2	0/1			9/12	3/4
Pseudomonas sp.	1/1		2/2	1/1		1/1			1/1		4/4	2/2
S. pyogenes			2/2								2/2	
S. pneumoniae	8/8	4/4		0/1	4/4	2/2					12/12	6/7
B. hemo strep		1/1		1/1								2/2
Enterococci		1/1										1/1
S. aureus	3/3	3/3		1/1	1/1	1/1		1/1			4/4	6/6
Total Eradicated	44	42	12	9	13	12	0	2	1	-	70	65
Total Evaluable	45	42	12	10	15	12	2	4	1	0	75	68
% Eradicated	97.8%	100%	100%	90%	86.7%	100%	-	-			93%	95.5%

Bacterial septicemia was diagnosed in 21 of Dr. Zellner's patients, nine in the 0.5 g dose group and twelve in the 1.0 g dose group. Seven pathogens were isolated in the 0.5 g dose group and ten in the 1.0 g dose group. Sixteen pathogens were qualified and all were eradicated. The most frequently isolated pathogen was E. coli.

The applicant's clinical cure rates for this study were 69% (58 of 84 qualified cases) for the 0.5 gram dose group and 66% (54 of 81 qualified cases) for the 1.0 gram dose group. For lower respiratory diseases the

bacteriological cure rates were 93% (70 of 75 strains) for the 0.5 gram dose group and 95.5% (65 of 68 strains) for the 1.0 gram dose group. There was a 100% cure for the 16 evaluable bacterial septicemia cases.

The applicant concludes that these dosage regimens are equally effective in the treatment of hospitalized patients with lower respiratory tract infections.

Reviewer's Comments:

1. Although the protocol stated that the treatment period should not exceed 14 days, the medical officer did not disqualify patients who were treated for 15 days.

2. The following patients are disqualified by the medical officer because the minimum treatment period of five days was not attained:

1.0 gram dose - Case #0173-026 - 3 days (Dr. Nolen)
0.5 gram dose - Case #0140-004 - 3 days (Dr. Eron) Also, this patient was discharged on IV tobramycin which was sequential therapy that interfered with the evaluation of outcome.

3. The medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

0.5 g	Nolen #0173-031	S. pneumoniae	cure	p. 11-147
1.0 g	Nolen #0173-015	H. influenzae	cure	p. 11-150
0.5 g	Zellner #0144-016	P. mirabilis	cure	p. 11-184
0.5 g	Zellner #0144-017	E. coli	cure	p. 11-184
1.0 g	Zellner #0144-012	H. influenzae	cure	p. 11-186
1.0 g	Zellner #0144-020	Klebsiella sp.	cure	p. 11-186
0.5 g	Snow #0143-036	S. pneumoniae	cure	p. 11-216

4. It should be noted that the applicant's table on page 46-080 omitted Dr. Eron's two 0.5 gram courses. These two cases were included in the above table showing that the total cure rate for the 0.5 gram group was 93% instead of 95.5% as given on page 46-080.

b) Study No. CAZ-R11 Franz Muhar, M.D., Vorstandder II hunger, Abt des Pulmologische Zentrum, Wien, Austria (Pulmonary Center, Vienna, Austria), conducted a randomized controlled clinical trial comparing two doses of ceftazidime in the treatment of lower respiratory tract infections in 30 patients in a study similar to the one described above. However, ceftazidime was given in doses of 0.5 g or 1.0 g every 12 hours.

	0.5 g bid	1.0 g bid
Diagnosis		
Bronchitis	9	14
Pneumonia	5	2
Total	14	16
Mean Age (yrs)	56.6	62.3
Sex Male	14	16
Female	0	0
Mean Length of Treatment (days)	6.6	7.2
% with Concurrent		
Pulmonary Dis.	21.4%	50.0%
Neoplasia	21.4%	12.5%
Clinical Response		
Cured	4 (28..6%)	6 (40.0%)
Improved	8	8
Failure	2	1
Bacteriological Response		
# Isolates Qual.	13	19
# Eradicated	12 (92.3%)	17 (89.5%)

The applicant concludes that the data from this very small single study adds information regarding twice daily dosing and cure rates are similar to thrice daiy dosing.

Reviewer's Comment: The medical officer disqualifies all of Dr. Muhar's cases from the bacteriological evaluation because none of his isolates were tested for susceptibility to ceftazidime (pages 11-263 to 11-267). The following organisms should be subtracted from the applicant's total.

	0.5 g bid	1.0 g bid
E. coli	1/1	1/2
Klebsiella sp.		1/1
P. mirabilis	1/1	
Proteus sp.		1/1
H. influenzae	2/2	2/2
Hemophilus sp.	3/3	6/6
Aeromonas	1/2	1/2
S. pneumoniae	4/4	5/5

2. Skin and Skin Structure Infections

Study No. CAZ-S01 A randomized controlled multiclinic trial comparing two doses of ceftazidime in the treatment of skin and skin structure infections was conducted at six clinical centers. Adult hospitalized patients received either 0.5 gram or 1.0 gram of ceftazidime intravenously every eight hours for 3-10 days. Exclusions and pretreatment studies were similar to those given above. Patients were to be evaluated daily.

To be considered evaluable a culture from the site of the infection was to have been obtained within 48 hours of the start of therapy. Isolates were tested for susceptibility to ceftazidime. Patients were to be evaluated daily. Cultures and susceptibility testing were to be repeated between the second and fourth day of treatment, and between 24 and 48 hours after treatment was discontinued. If culture material was not available, a bacteriological cure was considered. The clinical outcome was assessed as cured, improved, failed, or unevaluable. The bacteriological outcome was assessed as cured (initial pathogen eradicated after treatment or during treatment with a clinical cure after treatment) failed, cured with superinfection, or failure with superinfection and unevaluable.

Investigators were

Rodney M. Snow, M.D., Norwood Clinic, Birmingham, AL.

William J. Mogabgab, M.D., Department of Medicine, Tulane University School of Medicine, New Orleans, LA.

Lawrence Charles Parish, M.D., Paddington Testing Co., Inc., Philadelphia, PA.

Lawrence J. Eron, M.D., Infectious Diseases, Fairfax, VA.

Joseph J. Timmes, M.D., Department Surgery, Jersey City Medical Center, Jersey City, NJ.

Layne O. Gentry, M.D., Director, Infectious Disease Laboratory, Ben Taub Hospital, Houston, TX.

Two of Dr. Snow's patients with septicemia were clinical cures and one had a bacteriological cure. Seven patients in Dr. Mogabgab's groups who also had a diagnosis of bone and joint infection due to S. pyogenes (4 pts.), S. aureus (1), Enterobacter species (1), and P. aeruginosa (1) were cured. Four patients had bursitis and one had septic arthritis.

In Dr. Timmes' study 29 of the 36 patients received ceftazidime intramuscularly rather than intravenously. Most of his patients were drug abusers or were suspected of being drug abusers and it was the policy to avoid intravenous therapy to eliminate the possibility of the patient's self-administration of substances through intravenous lines.

In the following tables the bacteriological response gives the number of qualified pathogens eradicated over the number of qualified isolates.

0.5 gram Dose - Skin and Skin Structure Infections

	Snow	Mogabgab	Parish	Eron	Timmes	Gentry	Total
No. Patients	22	31	15	13	17	8	106
Age (yrs)							
Under 18	1	-	-	-	-	-	1
18-25	3	9	-	4	5	3	24
26-35	2	11	2	1	6	1	23
36-50	1	7	4	2	5	1	20
51-65	6	3	3	1	-	3	16
Over 65	9	1	6	5	1		22
Mean (yrs)	59.5	43.5	59.3	49.0	33.2	39.3	44.2
Sex M	8	23	2	9	12	6	60
F	14	8	13	4	5	2	46
Mean Duration (Days)	7.3	7.1	*12.7	*13.5	7.5	9.5	
Clinical Response							
Skin ulcer	1	-	10	2	1	1	15
Cellulitis	14	5	1	1	3	1	25
Abscess		3			6		9
Wound Infection		4		2		1	7
Other		3		1			4
Unspecified			1				1
Total Cured	15	15	12	6	10	3	61
Cured & Improved	17	17	15	9	15	4	77
Failures	0	0	0	1	0	0	1
% Cured	88.2%	88.2%	80%	60%	66.7%	75%	78.2%
Bacteriological Response							
E. coli		1/1	1/1	-	2/2	1/1	5/5
Klebsiella sp.		1/1		1/1		0/1	2/3
P. mirabilis	1/1		4/4			1/1	6/6
Proteus sp. indole	2/2		1/1	2/2			5/5
Enterobacter sp.	1/1	2/2		0/2		1/1	4/6
P. aeruginosa	0/1		3/3	5/5		2/2	10/11
Acinetobacter			1/1				1/1
S. pyogenes	2/2	3/3	1/1			1/1	7/7
S. aureus	1/4	6/6	5/8	1/1	0/3		13/20
Other	2/2	1/2	3/3	2/2	1/1		10/10
Total Eradicated	9	15	19	11	3	6	63
Total Evaluable	13	15	22	13	4	7	74
% Eradicated	69.2%	100%	86.4%	84.6%		85.7%	85.1%

1.0 gram Dose - Skin and Skin Structure Infections

	Snow	Magabgab	Parish	Eron	Timmer	Centry	Total
No. Patients	24	30	15	12	19	7	108
Age (yrs)							
Under 18	-	-	-	-	-	1	1
18-25	5	11	-	2	4	2	24
26-35	4	9	-	1	6	1	21
36-50	3	5	2	1	5	-	16
51-65	2	3	3	2	2	3	15
Over 65	10	2	11	6	1	1	31
Mean (yrs)	52.8	34.3	68.8	54.8	36.3	44.6	46.8
Sex M	10	21	2	8	13	7	61
F	14	9	14	4	6	0	47
Mean Duration (Days)	7.6	8.7	15.0	21.6	7.4	13.3	
Clinical Response							
Skin ulcer	2	-	8	-	-	-	10
Cellulitis	9	10	1		5	2	27
Abscess	1	-			4		5
Wound Infection	1	-		3	1		5
Other	1	1	3				5
Unspecified							-
Total Cured	14	11	12	3	10	2	52
Cured & Improved	16	17	16	8	16	4	77
Failures	0	0	0	0	1	0	1
% Cured	87.5	64.7	75	37.5	58.8	50	66.7

(Note: In the table on page 28, and in other tables, the number of patients at the top of the table represents the number of patients who were enrolled and includes both evaluable and unevaluable patients. Mogabgab enrolled 31. Of these 31, 17 were qualified for clinical response (add "Cured & Improved" and "Failures" to get the total qualified for clinical response) and 155 were qualified for bacteriological response. Fifteen of the 17 had complete symptomatic cures and two were only improved. There were no failures. This was done to shorten the table so that it would fit on one page.) Eron had 6 symptomatic cures, 3 symptomatic improvements, one failure, and three were disqualified. The total evaluable for the bacteriological response may be larger than the number enrolled because of polymicrobial infections.)

1.0 gram Dose - Skin and Skin Structure Infections

Bacteriological Response	Snow	Magabgab	Parish	Eron	Timmes	Gentry	Total
E. coli		1/1	4/4	2/2	1/1	1/1	9/9
Klebsiella sp.	1/1	1/1	1/1	2/2		1/1	6/6
P. mirabilis			8/8	1/3	1/1	1/1	11/13
Proteus (indole +)		1/1			0/1		1/2
Enterobacter sp.					1/1		1/1
P. aeruginosa	2/2		8/8	1/2		1/1	12/13
Acinetobacter			1/1	1/1			2/2
S. pyogenes	1/1	5/6			3/3	1/1	11/11
S. aureus	4/5	4/4	5/6		3/3	1/1	17/19
B hem Strep	2/2		3/3				5/5
Other	4/4	4/4	7/7				15/15
Total Eradicated	14	17	37	7	9	6	90
Total Evaluable	15	17	38	10	10	6	96
% Eradicated	93.3%	100%	97.4%	70%	90%	100%	93.8%

The applicant concludes that both doses given every eight hours for the treatment of skin and skin structure infections are equally effective with the possible exception of infections due to Staphylococcus aureus. At least a 1.0 gram dose will be required for this infection. Bacteriological cure rates were 85.2% for the 0.5 g dose and 94% for the 1.0 g dose.

Reviewer's Comments

1. It is noted that in Dr. Parish's study, the treatment period exceeded the ten-day maximum allowed in the protocol for 11 of 15 patients in the 0.5 gram dose group and for 12 of 16 patients in the 1.0 gram dose group. Also, of these patients with long treatment periods, two 0.5 gram group patients and five 1.0 gram group patients received ceftazidime intramuscularly rather than by the intravenous route as directed.

2. It is noted that in Dr. Eron's study, the treatment period exceeded the ten-day maximum allowed in the protocol for 7 of 13 patients in the 0.5 gram dose group and 10 of 12 patients in the 1.0 gram dose group. One applicant-qualified patient was treated for 37 days.

3. There are two errors in Table 28 on page 109 of Volume 46. In the 1.0 gram dose side of the table, 12 of 14 evaluable P. mirabilis isolates were eradicated instead of 11 of 13. Also, there was only one evaluable indole positive Proteus isolate and this was a failure.

4. The medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not tested:

0.5 g	Snow	#0143-012	S. aureus	cure	p 12-081
0.5 g	Parish	#0174-024	S. aureus	cure	p 12-143
0.5 g	Eron	#0140-016	Serratia sp	failure	p 12-173
0.5 g	Timmes	#0026-005	S. pyogenes	cure	p 12-203
0.5 g	Timmes	#0026-011	S. aureus	cure	p 12-203
0.5 g	Timmes	#0026-014	S. aureus	cure	p 12-203
0.5 g	Timmes	#0026-023	Peptostrepto-coccus	cure	p 12-203
1.0 g	Snow	#0143-008	S. aureus	cure	p 12-083
1.0 g	Timmes	#0026-002	Klebsiella sp	cure	p 12-205
1.0 g	Timmes	#0026-003	S. aureus	cure	p 12-205
1.0 g	Timmes	#0026-017	S. pyogenes	cure	p 12-205

The applicant amended the summary tables to show these additional disqualifications.

3. Urinary Tract Infections

a) Study No. CAZ-U01 and U02 In study No. U01, a randomized controlled trial comparing three doses of ceftazidime in the treatment of uncomplicated or complicated urinary tract infections was conducted at three clinical centers. Hospitalized adult patients were randomly assigned to three groups to receive either 0.25 g, 0.5 g, or 1.0 g of ceftazidime intramuscularly every 12 hours by the intramuscular route for 3-10 days. Study No. U02 was the same except that ceftazidime was given intravenously.

The protocol complied with the guidelines for the study of urinary tract infections established by FDA's Anti-Infective Drug Advisory Committee.

Investigators were

Stacy J. Childs, M.D., Southeastern Research Foundation, Inc., Alabaster, Alabama (Study No U01),

Paul O. Madsen, M.D., Chief of Urology, Veterans Administration Hospital, Madison WI (Study No U01),

Rodney M. Wishnow, M.D., Infectious Disease Division, Long Beach VA Hospital, Long Beach, CA (Study No U01), and

Layne O. Gentry, M.D., Director, Infectious Disease Laboratory, Ben Taub Hospital, Houston, Texas (Study No U02).

Urinary Tract Infections

	Childs			Madsen			Wisrow			Gentry		
	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0
No of Pts.	19	21	20	13	14	14	5	5	5	16	18	16
% Complicated	60	60	60	100	100	100	80	100	50	0	16	0
Age (yrs)												
under 18	-	-	-	-	-	-	-	-	-	-	-	-
18-25	5	2	-	-	-	-	-	-	-	8	7	9
26-35	3	6	7	-	-	-	-	-	-	5	4	6
36-50	1	3	6	-	-	2	-	-	2	3	4	1
51-65	3	4	3	4	5	5	2	4	-	-	3	-
Over 65	7	6	4	9	9	7	3	1	3	-	-	-
Mean	48.5	49.5	46.6	73.0	71.1	63.2	71.0	64.	62.2	28.6	33.0	26.4
Sex M	5	8	4	13	14	13	5	5	5	1	1	1
F	14	13	16	0	0	1	0	0	0	15	17	15
Mean duration (days)	4.3	4.5	4.9	6.4	7.1	6.9	7.0	7.4	6.6	6.0	5.9	5.6

The applicant concludes that these results suggest that the three-twice daily dosage regimens are effective both bacteriologically and clinically. It was decided, however, to use the 0.5 g and 1.0 g doses in comparative trials because of the incidence of superinfections in the 0.25 gram dose group. Five colonizations were found in the 0.25 gram group, two in the 1.0 gram group but none in the 0.5 gram group.

Urinary Tract Infections - Outcome (U01)
(Qualified Patients only)

	0.25 g dose	0.5 g dose	1.0 g dose
Clinical Response			
No. Qualified Pts.	45	45	44
No. cured			
Cystitis	19	21	20
Unspec. UTI	-	-	-
Pyelonephritis	16	18	14
Ureteritis	-	1	-
Total cured	35	40	35
Cured & Improved	44	45	44
Failures	1	0	0
% Cured	77.8	88.9	79.5
Bacteriological Response*			
E. coli	13/14	21/22	28/30
Klebsiella species	3/3	3/3	1/2
P. mirabilis	4/5	5/5	-
P. aeruginosa	2/3	2/2	2/4
Proteus species	2/2	-	0/1
Enterobacter sp.	2/2	1/1	1/1
Other	7/8	9/9	9/9
Total Eradicated	32	39	41
Total Evaluable	36	40	47
% Eradicated	88.9	97.5	87.2

*Number of qualified pathogens eradicated/ Number of qualified pathogens.

Reviewer's Comment: The medical officer disqualifies the following applicant-qualified isolate from the bacteriological evaluation because susceptibility was not reported: 0.5 g group, Dr. Childs, Case #C004-016, Diphtheroids, cure, p 13-072.

b) Study No. CAZ-U13 A randomized controlled trial of two doses of ceftazidime in the treatment of urinary tract infections was conducted by G. K. Daikos, M.D. at King Paul's Hospital in Athens, Greece. Thirty five adult patients were randomly assigned to two groups to receive either 500 mg or one gram of ceftazidime either intramuscularly or intravenously every 12 hours for up to two weeks. The protocol differs from the one above which followed FDA guidelines for the study of urinary tract infections. In this study urine cultures were obtained 24-48 hours after the final ceftazidime injection and again during a two-week follow-up period. Patients who had been admitted with urinary tract infections or who developed UTI's as a complication of some

other reason for admission, including surgical operations, were selected. All cases were diagnosed as pyelonephritis.

	0.5 g	1.0 g
No of patients	17	18
Mean age (yrs)	47.5	57.7
Sex M	10	10
F	7	8
Mean duration of therapy (days)	9.9	10.2
Clinical Outcome		
No. Cured	17 (100%)	18 (100%)
Bacteriological Outcome*		
E. coli	9/9	13/13
Klebsiella sp.	2/3	
P. mirabilis	1/1	
P. aeruginosa	1/3	1/1
Other	2/2	1/1
Total Eradicated	15 (83.3%)	15 (100%)
Total Evaluable	18	15

*Number of qualified pathogens eradicated/ Number of qualified pathogens isolated

The applicant concludes that 0.5 g doses twice daily are as effective as 1.0 g doses twice daily for the treatment of E. coli pyelonephritis.

Reviewer's Comment: The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

0.5 g	Daikos	# E025-422B	P. aeruginosa	Failure	p 13-242
0.5 g	Daikos	# E025-425B	Staphylococcus sp	Cure	p 13-242
0.5 g	Daikos	# E025-426B	E. coli	Cure	p 13-242
1.0 g	Daikos	# E025-423B	E. coli	Cure	p 13-244
1.0 g	Daikos	# E025-424B	E. coli	Cure	p 13-244

CONTROLLED CLINICAL TRIALS - ACTIVE DRUG COMPARISONS

1. Lower Respiratory Tract Infections and/or Septicemia

a) Study No. CAZ-RC3 A randomized controlled multiclinic trial comparing 1.0 g of ceftazidime with 1.0 g of cefamandole in the treatment of lower respiratory tract infections and/or systemic bacterial infections was conducted at nine clinical centers. The protocol is the same as the one described above under dose ranging studies except that 1.0 g of cefamandole every 6 hours replaces the low ceftazidime dose. Ceftazidime was given every 8 hours.

Investigators are listed below.

Thomas M. Nolen, M.D., Columbiana Clinic, Columbiana, AL,

Bienvenido G. Yangco, M.D., V.A. Medical Center, Tampa, FL,

Charles J. Schleupner, M.D., Chief of Infectious Disease Section, V.A. Medical Center, Salem, VA,

H. Preston Holley, M.D., Infectious Diseases and Immunology Division, Medical University of South Carolina, Charleston, SC,

Eskild A. Peterson, M.D., Ass't Prof. of Internal Medicine; Section on Infectious Diseases, Arizona Health Science Center, Tucson, AZ,

William H. Greene, M.D., Asso. Prof. of Medicine, Yale University School of Medicine, New Haven, CT,

Edward S. Johnson, M.D., Ass't Director Infectious Diseases, St. Michael's Medical Center, Newark, NJ,

Timothy W. Lane, M.D., Moses H. Cone Memorial Hospital, Greensboro, NC, and

Gary I. Levine, M.D., East Carolina Family Practice Center, Greenville, NC.

Lower Respiratory Tract Infections*

	Nolen		Yangco		Schleupner		Holly		Peterson		Greene		Johnson		Lane		Levine	
	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD
Total	48	47	30	28	11	9	8	8	7	6	6	6	7	8	3	3	4	3
Age (yrs)																		
Under 18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18-25	1	4	-	-	-	-	2	1	-	-	-	1	1	1	-	1	-	-
26-35	1	-	-	1	-	1	-	-	-	-	1	-	-	2	-	1	-	-
36-50	8	7	3	1	1	2	2	3	-	-	2	1	-	1	-	1	1	1
51-65	16	8	16	14	5	3	2	1	1	3	2	3	4	3	1	-	-	1
Over 65	22	28	11	12	5	3	2	3	6	3	1	1	2	1	2	-	3	1
Mean (yrs)	62.7	64.4	62.2	66.3	62.0	59.9	50.1	56.4	73.0	69.2	52.3	53.5	55.6	47.9	51.3	31.3	68.8	58.0
Sex M	26	21	30	28	11	9	2	5	5	2	3	6	4	5	3	2	3	2
F	22	26	0	0	0	0	6	3	2	4	3	0	3	3	0	1	1	1
Mean Duration (Days)	6.1	5.9	7.9	7.3	8.9	9.3	8.8	9.4	6.7	5.2	6.8	5.2	5.4	7.9	5.7	5.3	7.0	4.0
% with Concurrent Disorders-																		
Cardiovascular	54.2	51.1	36.7	35.7	9.1	22.2	37.5	37.5	42.9	33.3	33.3	16.7	14.3	37.5	33.3	0	50.0	33.3
Pulmonary	60.4	46.8	50.0	39.3	54.5	55.6	25.0	37.5	71.4	50.0	66.7	16.7	57.1	25.0	33.3	0	50.0	33.3
Clinical Outcome																		
# pts Qual.	47	45	24	23	11	7	7	6	7	4	4	4	5	8	2	3	4	2
% cured	68.1	37.8	65.2	65.2	81.9	85.7	85.7	66.7	100	100	25	25	60	62.2	2/2	2/3	1/4	1/2
Bacteriological Outcome																		
# Pathogens Qualified	32	21	29	22	7	12	5	6	7	2	3	4	4	1	2	0	3	4
% Eradicated	87.5	57.1	96.6	86.4	100	91.7	100	100	100	2/2	2/3	100%	100%	1/1	2/2	-	3/3	3/4

*Applicant's uncorrected analysis

Lower Respiratory Tract Infections - Outcome

	Applicant		Medical Officer	
	Ceftazidime	Cefamandole	Ceftazidime	Cefamandole
Clinical Response				
No. qualified pts.	112	99	112	99
No. cured	69	51	69	51
Pneumonia	6	2	6	2
Bronchitis	1		1	
Other	76	53	76	53
Total Cured	112	99	112	99
Cured & Improved	67.9%	53.5%	67.9%	53.5%
%Cured				
Bacteriological Response*				
E. coli	17/19	6/6	16/18	5/5
Klebsiella sp	9/9	10/13	9/9	10/13
P. mirabilis	7/7	2/5	7/7	2/5
Enterobacter sp	3/4	3/8	3/4	3/8
Citrobacter	2/2	0/1	2/2	0/1
H. influenza (+Amp.P)	8/8	8/8	9/9	7/7
S. pneumoniae	14/14	12/12	14/14	12/12
P. aeruginosa	3/5		3/5	
S. aureus	3/4	2/3	3/4	2/2
Other	5/6	4/4	3/4	4/4
Total Eradicated	71	47	71	45
Total Qualified	78	60	78	57
% Eradicated	91.0%	78.3%	91.0%	78.9%
Total Number of patients	124	118	124	118

*Number of qualified isolates eradicated/Number qualified isolated.

The age-sex distribution between the two groups was similar. The duration of treatment varied from two days to up to 21 days. For fifteen patients who were treated less than three days, the treatment regimen was changed because of improper diagnosis or inadequate antimicrobial coverage. The majority of patients from whom pathogens were isolated, had one isolate each. However, slightly more than 20% in each group had polymicrobial infections. Ceftazidime appeared to be more effective in eradicating Klebsiella strains, P. mirabilis, and Enterobacter species. It was active against P. aeruginosa whereas cefamandole had no antipseudomonal activity. Ceftazidime was as active as cefamandole in eliminating S. aureus although its MIC is 8 mcg/ml compared to 0.5 mcg/ml for cefamandole.

One ceftazidime-treated patient had bacterial septicemia and was cured clinically and bacteriologically. Three cefamandole-treated patients had bacterial septicemia. Two were cured and one improved.

When the applicant's bacteriological cure rates are compared, 91.0% for ceftazidime and 78.3% for cefamandole, cure rates suggest that ceftazidime is at least as effective as cefamandole at a smaller dose (less frequently-given dose) in the treatment of lower respiratory tract infections due to susceptible organisms listed. The same comparison can be made of symptomatic cure rates, 93.8% of ceftazidime cases cured or improved compared with 89.9% of cefamandole cases cured or improved. The differences between rates were not statistically significant.

Reviewer's Comment:

In the review of the original submission, the medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Nolen	#0173-022	S. pneumoniae	cure	p 14-109
Yangco	#0185-007	E. coli	cure	p 14-145
Yangco	#0185-010	S. pneumoniae	cure	p 14-145
Yangco	#0185-010	H. influenzae	cure	p 14-145
Yangco	#0185-011	H. influenzae	cure	p 14-145
Yangco	#0185-015	S. pneumoniae	cure	p 14-145
Yangco	#0185-021	H. influenzae	cure	p 14-146
Yangco	#0185-035	H. influenzae	cure	p 14-146
Yangco	#0185-041	Pseudomonas sp.	cure	p 14-146
Yangco	#0185-047	Enterobacter sp.	cure	p 14-147
Peterson	#0204-013	H. influenzae	cure	p 14-206
Johnson	#0165-004	b hemo strep	cure	p 14-256
Lane	#0203-005	S. pneumoniae	cure	p 14-266
Lane	#0203-005	H. influenzae	cure	p 14-266

Cefamandole

Yangco	#0185-033	Streptococcus sp.	cure	p 14-149
Yangco	#0185-038	S. pneumoniae	cure	p 14-149
Yangco	#0185-048	H. influenzae	failure	p 14-149
Yangco	#0185-059	H. influenzae	cure	p 14-150
Holley	#0186-004	S. pneumoniae	cure	p 14-186
Peterson	#0204-006	H. influenzae	cure	p 14-207
Peterson	#0204-012	b hemo strep	cure	p 14-207
Greene	#0207-011	H. influenzae	cure	p 14-224
Johnson	#0165-006	S. aureus	failure	p 14-257
Johnson	#0165-006	b hemo strep	failure	p 14-257
Johnson	#0165-012	E. coli	cure	p 14-257
Johnson	#0165-015	S. pneumoniae	cure	p 14-257
Levine	#0194-007	Hemophilus sp.	Cure	p 14-283
Levine	#0194-007	Streptococcus sp	Cure	p 14-283

From the Chi-square testing of the medical officer's bacteriological cure rates, p = 0.07. The difference is not statistically significant.

b) Studies No. CAZ-R04 and CAZ-R07 A randomized controlled multiclinic tr[illegible] to compare ceftazidime and a regimen of tobramycin plus ticarcillin in the treatment of serious lower respiratory tract infections was conducted at ten clinical centers. Hospitalized adult patients were randomly assigned to two treatment groups as follows:

2.0 g of ceftazidime every 8 hours IV or

1.5 mg/kg of tobramycin IV every 8 hours (adjusted to produce peak levels of greater than 8 mcg/ml and trough levels of less than 4 mcg/ml) and 3.0 g of ticarcillin IV every 4 hours.

The minimum treatment period was five days.

A 2.0 gram ceftazidime dose was selected because this study was designed to treat seriously ill compromised patients for whom it was believed that a concentration above or equal to the MIC of expected pathogens needed to be present in the blood throughout the dosing interval.

As with other lower respiratory tract infection studies, the diagnosis was confirmed by a positive pre-treatment culture of bronchopulmonary secretions and by chest X-ray. Bacterial septicemia was confirmed by the presence of the pathogen in at least two pre-treatment blood cultures. Thirty microgram discs were used for susceptibility testing.

The list of exclusions, besides those given above, included the exclusion of patients with infected devices (heart valves, infusion catheters, etc.) which could be removed or replaced. Patients were evaluated daily during treatment. Clinical and bacteriological outcomes were evaluated as described above.

The following eleven investigators participated in this study:

Thomas M. Nolen, M.D., Columbiana Clinic, Columbiana, AL,

Alfred Byron Young, M.D., Chairman, Department of Neurosurgery, University Hospital, University of Kentucky, Lexington, KY,

Lawrence A. Cone, M.D., Chief, Section of Immunology and Infectious Diseases, Eisenhower Medical Center, Rancho Mirage, CA,

James J. Rahal, Jr., M.D., Chief of Infectious Diseases, Manhattan V.A. Medical Center, New York, NY,

Kenneth Tack, M.D., Assistant Director of Internal Medicine, Saginaw Cooperative Hospitals, Saginaw, MI,

Jerrold J. Ellner, M.D., Director Division of Infectious Diseases, Department of Medicine, University Hospitals, Cleveland OH,

Marc Joseph Gurwith, M.D., Department of Medicine and Microbiology, Michigan State University, East Lansing, MI,

Joseph S. Solomkin, M.D., University of Cincinnati College of Medicine, Cincinnati, OH,

Donna Mildvan, M.D., Hospital Epidemiologist, Beth Israel Medical Center, New York, NY,

Burt R. Meyers, M.D., Department of Infectious Diseases, Mt. Sinai Medical Center, New York, NY, and

David N. Gilbert, M.D., Director of Medical Education and the Infectious Diseases Research Laboratory, Providence Medical Center, Portland, OR.

Dr. Gilbert conducted Study No. CAZ-R07. It differed from Study No. CAZ-R04 in that a loading dose of 1.8 mg/kg of tobramycin was given, and ticarcillin and ceftazidime doses were adjusted for impaired renal function. Patients could be enrolled if they had received other active antimicrobial therapy within up to 24 hours, instead of 48 hours, before the initiation of the test antibiotics.

In this study 123 patients were diagnosed as having lower respiratory tract infections and 20 patients were diagnosed as having bacterial septicemia. A single isolate was obtained from the majority of patients and one or more isolates were obtained from all but 17 patients. Fifty patients had polymicrobial infections. Eleven ceftazidime and nine tobramycin/ticarcillin patients had septicemia.

Serious Lower Respiratory Tract Infections (CAZ-R04 and CAZ-R07)*

	Nolen		Young		Cone		Rahal		Tack		Ellner		Gurwith		Solomkin		Mildvan		Meyers		Gilbert	
	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT
Total	18	17	17	18	19	17	1	2	2	2	1	2	1	1	4	4	3	1	1	0	6	6
Age (yrs.)																						
Under 18	18	17	18	19	19	17	1	2	2	2	1	2	1	1	4	4	3	1	1	0	6	6
18-25	-	-	3	4	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-
26-35	-	-	3	0	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
36-50	4	3	5	5	2	2	-	-	-	-	-	1	-	-	1	1	2	-	-	-	-	1
51-65	6	4	5	5	4	2	1	1	1	-	-	-	1	1	2	1	1	-	1	-	1	1
Over 65	8	10	2	3	13	13	-	1	1	2	-	-	-	-	1	1	-	1	-	-	5	4
Mean	62.8	69.6	44.6	43.8	67.4	70.3	61.0	64.1	66.0	06.0	23.0	31.0	51.0	62.0	53.8	52.8	61.7	76.0	56	-	75.8	70.3
Sex M	11	8	14	14	12	7	1	1	1	1	0	0	1	1	3	4	1	1	1	-	5	3
F	7	9	3	4	7	10	0	1	1	1	1	2	0	0	1	0	2	0	0	-	1	3
Mean Duration (Days)	6.4	6.5	7.3	8.6	7.9	7.2	14.0	15.5	8.5	5.5	6.0	3.5	7.0	9.0	7.0	14.0	11.7	3	1	-	9.3	9.7
% Concurrent Disorders																						
Cardiovasc.	38.9	41.2	29.4	0	57.9	0	0	(1)	0	(1)	(1)	0	(1)	0	25.0	50.0	0	0	0	-	100	50
Pulmonary	44.4	58.8	5.9	0	21.1	35.3	1/1	(1)	(1)	0	0	0	0	(1)	25.0	0	(1)	0	0	-	33.3	50
Clin. Outcome																						
# Pts Qualif.	17	17	12	18	12	10	1	1	2	1	0	0	1	1	3	4	3	0	0	-	100	50
% Pts Cured	64.7	70.6	25.0	33.3	75	50.0	1/1	0/1	2/2	0/1	-	-	0/1	0/1	2/2	2/4	3/3	-	0	-	33.3	50
Bacterio-logical Outcome																						
# Isolates Qualified	18	17	29	26	12	1	1	3	3	1	0	0	1	1	3	6	1	0	0	-	6	8
% Eradicated	94.4	94.1	72.4	66.7	100	1/1	1/1	1/3	3/3	1/1	-	-	0/1	1/1	3/3	83.3	1/1	-	-	-	100	87.5

*Applicant's uncorrected analysis

Lower Respiratory Tract Infections - Outcome (R04 and R07)

	Applicant		Medical Officer	
	Ceftazidime	Tobramycin/ Ticarcillin	Ceftazidime	Tobramycin/ Ticarcillin
Clinical Response				
No. pts qualified	62	59	54	59
No. pts cured				
Pneumonia	29	27	29	27
Bronchitis	1		1	
Unspecif. LRI	1	1	1	1
Pneumonitis		1		1
Total cured	31	29	31	29
Cured & Improved	48	52	48	52
% Cured	57.4	49.2	57.4	49.4
Bacteriological Response				
E. coli	8/8	9/10	8/8	9/10
Klebsiella sp	11/11	9/11	11/11	10/12
P. mirabilis	6/7	2/2	6/7	2/2
Proteus (indole+)	2/2		2/2	
Enterobacter sp	3/3	3/6	3/3	3/6
Citrobacter sp	2/2	0/2	2/2	0/1
Serratia sp	3/3	0/1	3/3	0/1
H. influenzae	6/6	9/10	6/6	9/9
P. aeruginosa	6/12	13/17	6/12	11/15
S. pneumoniae	5/5	2/3	5/5	2/3
S. aureus	3/4	3/5	3/4	3/5
Other	4/6	6/7	4/6	6/7
Total Eradicated	59	56	59	55
Total Isolates Qual.	69	73	69	71
% Eradicated	85.5%	76.7%	85.5%	77.4%
Total No. Pts.	62	61	62	61

The applicant concludes that the results of this multicenter trial indicate that ceftazidime, given as 2.0 grams every 8 hours intravenously, is as effective as the tobramycin/ticarcillin regimen used in this study. The difference between bacteriological cure rates is not statistically significant.

Reviewer's Comments

1. The reviewer does not agree with the applicant's evaluation of the bacteriological outcome for the following two cases:

#0272-003 A susceptible P. aeruginosa strain was isolated from the sputum on treatment days 1, 4, 8, 12, and 13 but not on the 15th

day. This represents one bacteriological cure for TNT instead of two as shown in the printout on page 15-245.

#0272-005 A susceptible P. aeruginosa strain was isolated from the sputum on treatment days 1 and 3 but not on the 7th day. This represents one bacteriological cure instead of two as shown in the printout on page 15-245.

2. These additional medical officer disqualifications do not alter the significance of the statistical evaluation of outcome rates.

3. In the review of the original submission, the medical officer disqualified the following applicant qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Cone	#0182-021	S. aureus	Cure	p 15-191
Cone	#0182-021	Acinetobacter	Cure	p 15-191
Cone	#0182-012	Achromobacter sp.	Cure	p 15-191
Cone	#0182-032	Klebsiella sp.	Cure	p 15-192
Solomkin	#0272-004	b hemo strep	Cure	p 15-244
Gilbert	#0188-006	Enterobacter sp.	Cure	p 15-321
Gilbert	#0183-006	P. mirabilis	Cure	p 15-321

Tobramycin/Ticarcillin

Young	#0190-004	H. influenzae	Cure	p 15-161
Young	#0190-009	Citrobacter	Failure	p 15-161
Young	#0190-009	H. influenzae	Failure	p 15-161
Young	#0190-017	H. influenzae	Cure	p 15-162
Young	#0190-034	b hemo strep	Cure	p 15-163

4. From the Chi-square testing of the medical officer's bacteriological cure rates, p = 0.2. The difference is not statistically significant.

c). Study No. CAZ-R08 Rodney M. Snow, M.D., Norwood Clinic, Birmingham, Alabama, conducted a randomized controlled trail of ceftazidime and moxalactam in the treatment of lower respiratory tract infections. Hospitalized adult patients received either 2.0 grams of ceftazidime or 2.0 grams of moxalactam intravenously every 12 hours for a minimum of five days. The study was similar to Study No. CAZ-R04, above.

	Ceftazidime	Moxalactam
No of patients	8	8
Mean age (yrs)	68.6	64.8
Sex M	6	5
F	2	3
Mean duration of therapy (days)	6.8	8.1
% with concurrent disorders		
Cardiovascular	62.5%	62.5%
Pulmonary	62.5%	25%
Clinical Outcome		
No pts qualified	5	7
No. Cured	5	6
Bacteriological Outcome*		
E. coli		1/1
P. mirabilis	1/1	
Enterobacter sp.		0/1
N. meningitidis		1/1
S. pneumoniae	1/1	2/2
b hem. strep	1/1	
Total	3/3	4/5

*Number of qualified pathogens eradicated/ Number of qualified pathogens isolated

The applicant concludes that these results suggest that ceftazidime is as effective as moxalactam in the treatment of lower respiratory tract infections, particularly when viewed in combination with other studies in this submission.

Reviewer's Comments: In Dr. Snow's study, the medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime	#0143-009	b hemo strep	Cure	p 15-364
Moxalactam	#0143-006	N. meningitidis	Cure	p 15-364

The applicant has included a section at the end of these four lower respiratory tract infection study reports (Volume 1.46, pages 99-103) which combines them in one overall analysis in which all ceftazidime-treated patients are compared with all active-control-drug treated patients. Since results of treatment with cefamandole, tobramycin/ticarcillin, and moxalactam cannot be combined, this comparison is not valid and is not acceptable.

2. Pneumonia

Study No. CAZ-R10 A randomized controlled multiclinic trial to compare ceftazidime and a regimen of tobramycin plus cefazolin or tobramycin plus ticarcillin in the treatment of lower respiratory tract infections was conducted at eight clinical centers in Canada. Hospitalized adult patients were randomly assigned to the following groups for treatment:

Ceftazidime -2.0 g q 8 h IV for 7 days to 3 weeks, or

If Pseudomonas species were absent,
Tobramycin - 1.7 mg/kg IV plus Cefazolin 1.5 g IV q 8 h for 7 days to 3 weeks,
If Pseudomonas species were present,
Tobramycin - 1.7 mg/kg IV plus Ticarcillin 3 g q 4 h IV for y days to 3 weeks.

Investigators are listed below.

Raymond Duperval, M.D., Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec.

Jean Vincelette, M.D., Hospital Saint-Luc, Montreal, Quebec.

Ronald Feld, M.D., The Princess Margaret Hospital, Department of Medicine, Toronto, Ontario.

Anita Rochelle Rachlis, M.D., Department of Medicine and Microbiology, Sunnybrook Medical Center, Toronto, Ontario.

Ignatius W. Fong, M.D., Ass't Professor of Medicine, University of Toronto, Toronto, Ontario.

Lionel A. Mandell, M.D., Henderson General Hospital, Hamilton, Ontario.

E. D. Ralph, M.D., Asso. Professor, University Hospital, University of Western Ontario, London, Ontario.

Allan Ross Ronald, M.D., Head of the Department of Microbiology, University of Manitoba, Winnepeg, Manitoba.

Of the 59 patients treated, only 44 patients were qualified for the clinical efficacy evaluation, and 29 isolates, 14 ceftazidime cases and 15 control cases divided between the two treatment groups were qualified for the bacteriological evaluation. This study is continuing and an updated report will be filed. This report is summarized in the amendment dated September 5, 1984 as shown below.

Canadian Pneumonia Study (CAZ-RIO)

Bacteriological Response*	Ceftazidime Alone	Tobramycin & Cefazolin	Tobramycin & Ticarcillin
E. coli	1/1	2/2	-
Klebsiella sp	3/3	1/2	1/1
Enterobacter sp	1/1	1/1	-
Serratia sp	1/1	0/1	-
Hemophilus (not flu)	1/1	0/1	-
P. aeruginosa	1/3	-	1/1
Pseudomonas sp	1/1	-	-
Moraxella sp	1/1	-	-
Pasteurella multocida	1/1		
S. aureus	0/1	4/4	-
Other	-	2/2	
Total Eradicated	11	10	2
No. Isolates Qualified	14	13	2
% Eradicated	78.6	76.9	(2/2)

*Number of qualified isolates eradicated/Number of qualified isolates.

Reviewer's Comment: Glaxo did not summarize this study in the original submission. No conclusions were drawn by the applicant because of the limited number of isolates. The microbiological data are supportive of other data.

3. Chronic Bronchopulmonary Infections due to Pseudomonas aeruginosa in Cystic Fibrosis Patients

a) Study No. CAZ-M43 Neils Hoiby, M.D. and Christian Koch, Rigshospitalet, Copenhagen, Denmark, conducted a randomized crossover trial of ceftazidime and a regimen of tobramycin plus carbenicillin in the treatment of chronic bronchopulmonary infections due to Pseudomonas aeruginosa in fibrocystic patients. Children and young adults were randomly assigned to receive either

Ceftazidime - 150 mg/kg/day IV for 15 days, or
Tobramycin - 10 mg/kg/day plus
Carbenicillin - 500 mg/kg/day IV for 15 days.

The 15 patients in the study ranged in age from 2 to 22 years. The mean starting age was 11.6 years. There were 11 males and four females. After three months each patient was crossed to the other treatment.

Clinically ten of ten evaluable ceftazidime patients and nine of nine evaluable control patients were classified as improved. Microbiologically, four of ten P. aeruginosa strains were eradicated in the evaluable ceftazidime patients and two of 14 were eradicated in the evaluable tobramycin/carbenicillin patients.

The applicant concludes that results suggest that ceftazidime is as effective as a regimen of tobramycin plus carbenicillin in the treatment of chronic pulmonary infections in fibrocystic patients. However, complete eradication of P. aeruginosa was not accomplished as is frequently the case. A better assessment of efficacy in this population is the clinical response which was 100% for both groups.

Reviewer's Comments:

1. Data from studies of pulmonary infections in patients with cystic fibrosis should not be used as evidence of drug efficacy. The purpose of the clinical investigation of new drugs is to measure the drug's ability to eradicate susceptible pathogens and, as is usually the case, eradication of the pathogen cannot be accomplished in patients with cystic fibrosis. These patients have impaired muco-cilliary clearance and colonization with P. aeruginosa is chronic. The organism can be found in the sputum of 64-87% of patients.

2. Of equal importance is the fact that a study with a crossover design is not acceptable for the evaluation of efficacy of an antibiotic because the first treatment period is bound to have an effect on the conditions of the second and upon the susceptibility/resistance status of the pathogenic organisms that colonize the respiratory tract in the second part of the cross.

3. There is no curriculum vitae for Dr. Hoiby and Dr. Koch's curriculum vitae has not been translated from the Danish language.

4. The random code which has been available in reports for other studies, is not available for this study.

b) Study No CAZ-M74 Neils Hoiby, M.D. and Christian Koch, from Denmark, conducted a second study in the treatment of chronic bronchopulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis. This study is the same as Dr. Hoiby's study No. CAZ-M43, above, except that the control drug was tobramycin alone.

Thirteen patients were enrolled. Ceftazidime eradicated 4 of 16 evaluable isolates and tobramycin was not effective against any of the 13 evaluable isolates. Clinically, none were cured but all were improved.

Reviewer's Comment: Same as above for Study No. CAZ-M43.

4. Skin and Skin Structure Infections

a) Study No. CAZ-S03 A randomized controlled multiclinic trial to compare ceftazidime and cefamandole in the treatment of skin and skin structure infections was conducted at ten clinical centers. Hospitalized adult patients were randomly assigned to receive either of the following regimens:

Ceftazidime - 1.0 g q 8 h IV for 3 to 14 days, or
Cefamandole - 1.0 g q 6 h IV for 3 to 14 days.

Pretreatment cultures of susceptible organisms were obtained by aseptic aspiration or by a swab of purulent material from the site of the infection. Bacterial septicemia was diagnosed by at least two pretreatment blood cultures and by symptoms which have been described above (Study CAZ-P01). Isolates were tested for their susceptibilities to ceftazidime and cefamandole.

As before, clinical outcome was assessed as cured, improved, or failed. Bacteriological outcome was classified as cure, failure, cure with superinfection, or failure with superinfection.

There were ten investigators in this study and they are listed below.

John E. Bottsford, M.D., Assistant Professor of Surgery, Spartanburg General Hospital, Spartanburg, SC,

Stephen R. Zellner, M.D., Clinical Physiology Associates, Fort Myers, FL,

Ronald Lee Nichols, M.D., Henderson Professor of Surgery, Tulane University Medical School, New Orleans, LA,

Layne O. Gentry, M.D., Director Infectious Disease Laboratory, Ben Taub Hospital, Houston, TX,

Peter A. Gross, M.D., Chief, Infectious Disease Section, Hackensack Medical Center, Hackensack, NJ,

William H. Greene, M.D., Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT,

Daniel J. Sexton, M.D., Oklahoma City Clinic, Oklahoma City, OK,

Timothy C. Fabian, M.D., Associate Professor of Surgery and Director of Trauma, University of Tennessee School of Medicine, Memphis, TN,

Edward S. Johnson, M.D., Assistant Director of Infectious Disease Service and Fellowship Program, St. Michael's Medical Center, Newark, NJ, and

Bienvenido G. Yangco, M.D., V.A. Medical Center, Tampa, FL.

The greatest number of disqualifications were due to surgical intervention at the site of the infection. Surgical intervention interfered with the evaluation of outcome. Many organisms were from abscesses which underwent incision and drainage. Thus, a bacteriological evaluation could not be made for these cases. Despite this, sufficient evaluable data were obtained to compare rates. Isolates of resistant organisms were disqualified from the efficacy evaluation. There was a high rate of resistance to cefamandole in some studies. Slightly more than 50% of patients in both groups had polymicrobial infections. Three patients in the ceftazidime group and one in the cefamandole group were treated intramuscularly instead of intravenously.

Skin and Skin Structure Infections (CAZ -S03)*

	Bottsford		Zellner		Nichols		Gentry		Gross		Greene		Sexton		Fabian		Johnson		Yango
	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ	CMD	CAZ
Total	29	27	20	15	26	27	12	13	6	4	5	6	6	5	22	23	5	5	6
Age (yrs)																			
Under 18	-	-	-	-	-	-	-	-											
18-25	1	3	1	1	4	3	5	3	1	1	1	-	2	1	9	9	-	-	-
26-35	9	6	2	1	8	7	3	3	1	-	1	1	-	-	7	4	2	1	-
36-50	3	5	2	1	3	7	4	3	1	-	-	1	-	1	4	9	1	1	3
51-65	9	6	8	3	8	8	-	4	-	-	1	1	1	-	2	1	-	2	2
Over 65	7	7	7	9	3	2	-	-	3	3	2	3	3	3	-	-	2	1	1
Mean (yrs)	51.4	49.7	57.1	63.5	43.3	43.7	31.7	39.5	50.8	63.5	52.6	59.5	53.3	56.0	31.8	33.0	51.0	51.2	51.2
Sex M	15	10	11	8	14	17	7	12	2	2	2	3	4	3	10	14	2	2	6
F	14	17	9	7	12	10	5	1	4	2	3	3	2	2	12	9	3	3	0
Mean Duration (Days)	7.7	7.9	14.6	6.9	5.5	6.3	7.0	12.5	10.5	8.5	14.0	5.2	14.2	14.8	4.5	5.1	16.8	9.4	13.0
Concurrent Disorders (%)																			
Diabetes	27.6	29.6	30.0	40.0	23.1	40.7	25.0	7.7	0	0	20.0	66.7	16.7	60.0	18.2	30.4	0	20.0	0
Alcoholism	24.1	14.8	0	0	0	3.7	16.7	30.8	0	0	0	0	0	0	0	4.3	20	0	16.7
Clinical Outcome																			
#pts Qual.	17	15	16	8	16	13	7	9	5	1	4	4	5	1	9	9	5	3	5
% Cured	94.1	86.7	93.8	100.0	93.8	100.0	57.2	88.9	80	1/1	0	0	80%	1/1	100	88.9	80	1/3	40
Bacteriological Outcome																			
# Qualified	25	18	20	4	23	23	7	11	6	1	4	0	5	1	6	7	3	1	9
% Eradicated	96.0	72.2	100	100	87	91.3	71.4	90.9	100	0/1	100	-	80	1/1	66.7	100.0	100	1/1	77.8

*Applicant's uncorrected analysis

Skin and Skin Structure Infections Outcome (CAZ - S03)

	Applicant		Medical Officer	
	Ceftazidime	Cefamandole	Ceftazidime	Cefamandole
Clinical Response				
No. pts Qualified	86	67		
No. cured				
Skin Ulcer	6	5		
Cellulitis	26	14		
Abscess	14	13		
Wound Infections	5	3		
Infected Digit	1	1		
Infected graft site	1	-		
Burn	1	-		
Infected gangrene	-	2		
Total cured	54 (62.8%)	38 (56.7%)		
Cured and Improved	78 (90.7%)	62 (92.5%)		
Bacteriological Response				
E. coli	5/6	3/3	5/6	3/3
Klebsiella species	6/7	3/4	6/7	3/4
P. mirabilis	11/12	6/8	11/12	5/7
Enterobacter sp.	4/4	3/3	4/4	3/3
P. aeruginosa	9/10	1/1	10/11	1/1
S. pyogenes	10/10	6/7	10/10	7/8
beta hemo. strep	6/7	3/3	6/7	3/3
S. aureus	21/14	17/22	20/23	20/25
Other	8/8	7/8	7/8	7/8
Total Eradicated	80	49	79	52
Total Isolates Qual.	89	59	88	62
% Eradicated	89.9%	83.1%	89.8%	83.9%
Total No. Pts.	129	123	129	123

The applicant concludes that ceftazidime is as effective as cefamandole in the treatment of skin and skin structure infections.

Reviewer's Comments

1. In the review of the original submission the medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Bottsford	#0187-008	Klebsiella sp.	Cure	p 17-123
Bottsford	#0187-015	S. pyogenes	Cure	p 17-123
Bottsford	#0187-019	S. pyogenes	Cure	p 17-123

Zellner	#0144-014	S. aureus	Cure	p 17-156
Zellner	#0144-008B	Proteus sp.	Cure	p 17-157
Nichols	#0022-049	Clostridium sp.	Cure	p 17-185
Nichols	#0022-049	Peptococcus	Cure	p 17-185
Nichols	#0022-049	B. fragilis	Cure	p 17-185
Nichols	#0022-049	Bacteroides	Cure	p 17-185
Nichols	#0022-049	E. coli	Cure	p 17-185
Gross	#0214-006	P. mirabilis	Cure	p 17-288
Sexton	#0276-005	S. aureus	Cure	p 17-255
Fabian	#0270-002	S. pyogenes	Cure	p 17-289
Fabian	#0270-002	S. aureus	Cure	p 17-289
Fabian	#0270-042	Peptococcus	Failure	p 17-290
Johnson	#0165-003	S. pyogenes	Cure	p 17-302
Yangco	#0185-004	P. aeruginosa	Failure	p 17-317
Yangco	#0185-011	Acinetobacter	Cure	p 17-317
Yangco	#0185-011	b hemo strep	Cure	p 17-317

Cefamandole

Bottsford	#0187-013	b hemo strep	Cure	p 17-126
Bottsford	#0187-039	P. mirabilis	Cure	p 17-128
Nichols	#0022-027	Bacteroides	Cure	p 17-187
Nichols	#0022-035	S. aureus	Cure	p 17-187
Fabian	#0270-041	B. fragilis	Cure	p 17-293
Fabian	#0270-043	Peptococcus	Cure	p 17-293
Fabian	#0270-043	B. fragilis	Cure	p 17-293
Yangco	#0185-008	Providencia	Failure	p 17-318

In response to the reviewer's request these isolates were disqualified in the September 1984 amendment to the application.

b) Study No. CAZ-S04 A randomized controlled multiclinic trial to compare ceftazidime and a regimen of tobramycin plus ticarcillin in the treatment of skin and skin structure infections was conducted at eight clinical centers. Hospitalized adult patients were randomly assigned to receive either of the following treatments:

Ceftazidime - 2.0 g q 8 h IV for 5 to 14 days, or
Tobramycin - 1.5 mg/kg q 8 h IV plus Ticarcillin - 3.0 g q 4 h IV for 5 to 14 days. The tobramycin dose was adjusted to produce peaks of 8 mcg/ml or higher and troughs less than 4 mcg/ml.

This protocol was similar to the one described above, No CAZ-S03.

The eight investigators are listed below:

Thomas M. Nolen, M.D., Columbiana Clinic, Columbiana, AL,

James J. Rahal, Jr., M.D., Chief of Infectious Diseases, Manhattan V.A. Medical Center, New York, NY,

Gordon M. Trenholme, M.D., Section on Infectious Diseases, Rush-Presbyterian St. Luke's Medical Center, Chicago, IL,

R. David Miller, M.D., OB-GYN Infectious Diseases, Un of CA Irvine Medical Center, Orange, CA,

Robert H. K. Eng, M.D., Infectious Disease Section, V. A. Medical Center, East Orange, NJ,

Joseph S. Solomkin, M.D., University of Cincinnati College of Medicine, Cincinnati, OH,

Evalea Glanges, M.D., Department of Surgery, John Peter Smith Hospital, Ft. Worth, TX, and

Burt R. Myers, M.D., Mt. Sinai Hospital, New York, NY.

Skin and Skin Structure Infections (CAZ -S04)*

	Nolen		Rahal		Trenholme		Miller		Eng		Solomkin		Glanges		Myers	
	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT
Total	15	15	2	2	9	4	8	10	10	7	7	7	8	9	0	1
Age (yrs)																
Under 18	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	3	-	-	-	1	-	-	2	-	-
26-35	1	2	-	-	2	-	-	2	1	1	-	1	1	1	-	1
36-50	3	2	-	-	1	-	3	4	2	-	1	1	1	2	-	-
51-65	5	3	-	1	5	2	-	1	4	4	2	5	1	4	-	-
Over 65	5	8	2	1	1	2	2	3	3	2	3	-	5	-	-	-
Mean (yrs)	56.1	61.7	72.0	73.0	52.4	56.5	41.6	50.9	56.7	55.3	57.0	52.9	53.5	44.3	-	41
Sex Male	9	8	2	2	5	0	0	0	-	-	3	2	4	7	-	0
Female	6	7	0	0	4	4	8	10	10	7	4	5	4	2	-	1
Mean Duration (Days)	6.5	6.9	22.5	10.5	16.3	22.0	4.5	6.4	9.6	7.6	11.6	9.9	8.8	5.4	-	4
Concurrent Disorders (%)																
Diabetes	20.0	33.3	0	0	11.1	25.0	12.5	0	70.0	71.4	28.6	57.1	25.0	44.4	-	-
Alcoholism	0	0	50	50	0	0	0	0	20.0	0	42.9	28.6	25.0	0	-	-
Clinical Outcome																
#pts Qual.	15	14	2	-	6	2	7	8	3	1	1	2	6	7	-	0
% Cured & Improved	100.0	85.7	2/2	-	100.0	100.0	71.4	75.0	3/3	1/1	1/1	2/2	100	85.7	-	-
Bacteriological Outcome																
# Isolates Qualified	22	16	0	0	7	2	0	1	2	1	7	1	3	10	-	0
% Eradicated	90.9	81.3	-	-	85.7	100.0	-	1/1	2/2	1/1	100.0	1/1	2/3	80	-	-

*Applicant's uncorrected analysis

Skin and Skin Structure Infections Outcome (CAZ - S03)

	Ceftazidime	Tobramycin/Ticarcillin
Clinical Response		
No. pts Qualified	42	35
No. of Cures		
Skin Ulcer	3	1
Cellulitis	11	7
Abscess	4	7
Wound Infections	3	5
Necrotic Ulcer	-	-
Infected gangrene site	-	-
Boil/Furunculosis	-	1
Total cured	21 (50.0%)	22 (62.9%)
Cured and Improved	78 (95.2%)	30 (85.8%)
Bacteriological Response*		
E. coli	3/4	2/3
P. mirabilis	3/3	1/3
Enterobacter species	6/6	1/1
Citrobacter species	2/2	-
P. aeruginosa	4/4	5/5
S. pyogenes	2/2	3/3
beta hemo. strep	2/2	1/2
S. aureus	5/6	10/11
Other	3/4	4/4
No. Eradicated	30	27
No. Isolates Qualified	33	32
% Eradicated	90.9%	84.4%
Total No. Pts.	59	55

*** Number of qualified isolates eradicated/ No. of qualified isolates.**

The applicant concludes that a 2.0 gram dose of ceftazidime every eight hours is at least as effective clinically and bacteriologically as the well-accepted regimen of tobramycin plus ticarcillin in the treatment of serious skin and skin structure infections.

Reviewer's Comment

1. In the review of the original submission, the medical officer disqualified the following seven applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Nolen	#0173-003	S. aureus	Cure	p 18-095

Nolen	#0173-023	Citrobacter	Cure	p 18-095
Nolen	#0173-023	P. aeruginosa	Cure	p 18-096
Solomkin	#0272-009	S. viridans	Cure	p 18-177
Glanges	#0271-011	Proteus sp.	Cure	p 18-195

Tobramycin/Ticarcillin

Nolen	#0173-021	S. aureus	Cure	p 18-098
Nolen	#0173-022	S. aureus	Cure	p 18-098

2. Based upon the reviewer's calculation, p = more than 0.317 for the eradication rates. Therefore, this study does not reveal a difference between groups.

c) Study No. CAZ-S07 A randomized controlled two-clinic trial to compare ceftazidime and moxalactam in the treatment of skin and skin structure infections was conducted by Rodney M. Snow, M.D., Norwood Clinic, Birmingham, AL, and Chien Liu, M.D., Director of the Division of Infectious Diseases, University of Kansas School of Medicine, Kansas City, KS. The protocol was the same as the two previous protocols except that patients were randomized to receive

Ceftazidime - 2.0 g q 12 h IV or
Moxalactam - 2.0 g q 12 h IV.

The minimum treatment period was 3 days and treatment continued for at least 48 hours beyond the time the patient had become asymptomatic, or to the time evidence of eradication had been obtained.

Skin and Skin Structure Infections (CAZ-S07)

	Snow		Liu	
	CAZ	MOX	CAZ	MOX
Total	23	24	4	6
Age (yrs.) Under 18	-	-	-	-
18-25	2	4	-	2
26-35	2	3	1	2
36-50	5	2	-	
51-65	5	4	1	1
Over 65	9	11	2	1
Mean (yrs.)	56.3	56.8	42.8	40.0
Sex Male	11	8	4	1
Female	12	16	0	5
Mean Duration (days)	11.8	8.9	11.3	8.7
Concurrent Disorders (%)				
Diabetes	56.5%	16.7%	25%	50%
Alcoholism	4.3%	4.2%	0	0
Clinical Outcome				
No. of pts. qualified	14	15	3	5
% Cured and Improved	85.7%	80.0%	(3/3)	80%
Bacteriological Outcome				
No. of isolates qualfied	17	16	3	4
% Eradicated	100%	100%	(3/3)	100%

The applicant concludes that these results indicate that ceftazidime is as effective as moxalactam in the treatment of skin and skin structure infections caused by susceptible pathogens.

Skin and Skin Structure Infections (CAZ-S07)

Bacteriological Response	Ceftazidime	Moxalactam
E. coli	1/1	3/3
P. mirabilis	2/2	1/1
Enterobacter species	1/1	2/2
Serratia species	1/1	1/1
P. aeruginosa	4/4	1/1
S. pyogenes	2/2	-
b hemo strep	3/3	0/1
S. aureus	5/5	5/5
Other	1/1	6/6
Total Eradicated	20	19
Total Isolates Qualified	20	20
% Eradicated	100%	95.0%

Reviewer's Comment:

In the review of the original submission, the medical officer disqualified the following nine applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported.

Ceftazidime

Snow	#0143-018	S. aureus	Cure	p 18-285

Tobramycin/Ticarcillin

Snow	#0143-007	S. aureus	Cure	p 18-287
Snow	#0143-007	E. coli	Cure	p 18-257
Snow	#0143-007	S. viridans	Cure	p 18-257
Snow	#0143-007	P. mirabilis	Cure	p 18-257
Snow	#0143-034	Serratia sp.	Cure	p 18-288
Liu	#0217-006	S. viridans	Cure	p 18-302
Liu	#0217-006	Propionibacterium	Cure	p 18-302
Liu	#0217-006	Bacteroides sp.	Cure	p 18-302

These disqualified cases have been deleted from the response table shown above.

5. Gynecological Infections

Study No. CAZ-S09 A randomized controlled comparison of ceftazidime and a regimen of tobramycin and clindamycin inthe treatment of gynecological infections was conducted at two clinical centers. Hospitalized patients with an oral temperature of 100.4°F or greater and with a clinical diagnosis of endometritis, salpingitis, or vaginal cellulitis, and who met the selection criteria received the same doses as those given below for intra-abdominal infections. Doses were

Ceftazidime 1.0 g q 8 h IV for at least 7 days, or
Tobramycin - 1.5 mg/kg IV q 8 h,
plus Clindamycin - 600 mg IV q 8 h for at least 7 days.

Pretreatment aerobic and anaerobic cultures obtained by either uterine lavage, direct aspirate, laparoscopy or culdocentesis were required.

Investigators were

Jorge D. Blanco, M.D., Department of Obstetrics and Gynecology, Un. of Texas Health Science Center at San Antonio, TX, and

Milagros Pagaduan Reyes, M.D., Section of Infectious Diseases, Hutzel Hospital, Detroit, MI.

Patients were assessed before treatment, at least once daily during treatment, and after treatment ended. Pretreatment specimens were obtained for hematology, chemistry, and urinalysis as in all of these studies.

GYNECOLOGICAL INFECTIONS (S09)

		Blanco		Reyes	
		CAZ	T-Clind	CAZ	T-Clind
Total		39	40	1	-
Age (yrs.)	Under 18	5	1	-	-
	18-25	27	27	1	-
	26-35	7	9	-	-
	36-50	-	3	-	-
	51-65	-	-	-	-
	Over 65	-	-	-	-
	Mean	22.0	24.0	23.0	-
Sex	Male	0	0	0	-
	Female	39	40	1	-
Mean Duration (days)		5.2	5.1	7	-
Concurrent Disorders (%)					
	Neoplasia	0	0	0	-
	Diabetes	0	7.5	0	-

GYNECOLOGICAL INFECTIONS (S09) - Continued

	Blanco		Reyes	
	CAZ	T-Clind	CAZ	T-Clind
Clinical Outcome				
No. pts. qualified	38	39	1	-
% Cured and Improved	92.1%	87.1%	(1/1)	-
Bacteriological Outcome*				
No. isolates qualified	61	64	1	-
% Eradicated	95.1%	95.3%	(1/1)	-

*Uncorrected applicant's analysis in the original submission

Gynecological Infections - Outcome (CAZ - S09)
(Drs Blanco and Reyes)

	Applicant		Medical Officer	
	CAZ	~~CAZ~~/Clind	CAZ	~~CAZ~~/Clind
Clinical Response				
No pts. Qualified	39	39		
No. Cured				
Endoparametritis	35	30		
Salpingitis	-	3		
Vaginal Cuff Cellulitis	1	1		
Total Cured (%)	36 (92.5%)	34 (87.2%)		
Bacteriological Response				
E. coli	11/11	10/12	11/11	10/11
Klebsiella species	3/3	5/5	3/3	5/5
P. mirabilis	2/2	2/3	2/2	2/3
b hemo. strep	6/6	2/2	6/6	1/1
S. aureus	2/2	1/1	2/2	1/1
Bacteroides (not frag.)	19/21	20/20	17/19	0/0
Peptostreptococcus	4/4	3/3	4/4	0/0
Peptococcus	3/4	1/1	3/4	0/0
Fusobacterium		7/7		0/0
Other	5/5	6/6	5/5	3/3
Total Eradicated	55	57	53	22
Total Qualified	58	60	56	24
% Eradicated	94.8%	95.0%	96.2%	91.7%

The applicant concludes that ceftazidime is as effective as the control regimen in the treatment of gynecological infections. Bacteriological cure rates were essentially the same.

Reviewer's Comment

1. In the reivew of the original submission, the medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported.

Ceftazidime

Blanco	#0229-003	Gardenerella	Cure	p 18-418
Blanco	#0229-024	Bacteroides	Cure	p 18-419
Blanco	#0229-048	S. aureus	Cure	p 18-420

Tobramycin/Clindamycin

Blanco	#0229-002	Bacteroides	Cure	p 18-423
Blanco	#0229-005	B. fragilis	Cure	p 18-423
Blanco	#0229-006	Bacteroides	Cure	p 18-423
Blanco	#0229-009	Bacteroides	Cure	p 18-423
Blanco	#0229-009	Peptostreptococcus	Cure	p 18-423
Blanco	#0229-011	Peptostreptococcus	Cure	p 18-423
Blanco	#0229-011	Bacteroides	Cure	p 18-423
Blanco	#0229-013	Bacteroides	Cure	p 18-423
Blanco	#0229-013	Fusobacterium	Cure	p 18-423
Blanco	#0229-013	Eubacterium	Cure	p 18-423
Blanco	#0229-015	Bacteroides	Cure	p 18-424
Blanco	#0229-020	Bacteroides	Cure	p 18-424
Blanco	#0229-022	Bacteroides	Cure	p 18-424
Blanco	#0229-025	Bacteroides	Cure	p 18-424
Blanco	#0229-027	b hemo strep	Cure	p 18-424
Blanco	#0229-028	b hemo strep	Cure	p 18-424
Blanco	#0229-028	Bacteroides	Cure	p 18-424
Blanco	#0229-031	Fusobacterium	Cure	p 18-425
Blanco	#0229-031	Clostridium	Cure	p 18-425
Blanco	#0229-033	Fusobacterium	Cure	p 18-425
Blanco	#0229-033	Bacteroides	Cure	p 18-425
Blanco	#0229-035	Peptostreptococcus	Cure	p 18-425
Blanco	#0229-035	Bacteroides	Cure	p 18-425
Blanco	#0229-039	P. mirabilis	Cure	p 18-425
Blanco	#0229-041	Fusobacterium	Cure	p 18-425
Blanco	#0229-041	N. gonorrhoeae	Cure	p 18-425
Blanco	#0229-043	b hemo strep	Cure	p 18-425
Blanco	#0229-047	Bacteroides	Cure	p 18-426
Blanco	#0229-050	Fusobacterium	Cure	p 18-426
Blanco	#0229-050	Bacteroides	Cure	p 18-426
Blanco	#0229-053	Bacteroides	Cure	p 18-426
Blanco	#0229-055	Bacteroides	Cure	p 18-426
Blanco	#0229-064	Fusobacterium	Cure	p 18-427
Blanco	#0229-066	Peptococcus	Cure	p 18-427
Blanco	#0229-066	Bacteroides	Cure	p 18-427

Blanco	#0229-068	b hemo strep	Cure	p 18-427
Blanco	#0229-072	Clostridium	Cure	p 18-427
Blanco	#0229-074	Bacteroides	Cure	p 18-428
Blanco	#0229-074	Fusobacterium	Cure	p 18-428
Blanco	#0229-077	Bacteroides	Cure	p 18-428

2. In Dr. Blanco's study, susceptibility testing of anaerobes was reported for the ceftazidime group but, curiously, not for the tobramycin/clindamycin group. Failure to study both groups equally is a protocol violation and reduces the validity of the study.

6. Intra-abdominal Infections

a) Study No. CAZ-508 Corstiaan Brass, M.D., Department of Medicine, The Buffalo General Hospital, Buffalo, New York, conducted a randomized controlled trial to compare ceftazidime with a regimen of tobramycin and clindamycin in the treatment of intra-abdominal infections. Hospitalized adult patients were randomly assigned to one of the following two treatment groups:

Ceftazidime - 2.0 g q 8 h IV for at least 7 days, or
Tobramycin - 1.5 mg/kg IV q 8 h
plus Clindamycin - 600 mg IV q 8 h for at least 7 days.

Patients with peritonitis, cholangitis, post-operative surgical wounds, bacteremia accompanying intra-abdominal infections, and patients with intra-abdominal or pelvic abscesses were enrolled. Appropriate cultures from the site of the infection were obtained within 48 hours of the start of treatment and were to be repeated within 2-4 days during treatment and 24-48 hours after treatment was discontinued when culture material was available. Isolates were tested for susceptibility.

Bacteriological Response

	Ceftazidime	Tobramycin/Clindamycin
E. coli	1/1	2/2
Klebsiella species	2/2	1/1
Enterobacter species		1/2
Total	3/3	4/5

	Intra-Abdom. Brass (#S08)		Surgical Stone (#S10)		Intra-Abdom. Gonzenbach (#M50)	
	CAZ	T/C1	CAZ	T/C1	CAZ	T/C1
Total	6	8	35	22	34	33
Age (yrs)						
Under 18	-	-	1	-	1	-
18-25	-	-	10	3	3	5
26-35	-	1	9	3	1	2
36-50	1	1	6	8	7	6
51-65	2	2	8	2	7	8
Over 65	3	4	1	6	15	12
Mean	64.5	59.4	37.0	49.0	58.4	55.1
Sex M	3	5	24	13	16	18
F	3	3	11	9	18	15
Mean Duration (Days)	13.5	15.3	7.8	7.8	9.1	8.5
Concurrent Disorders (%)						
Neoplasia	83.3	100	5.7	0	17.6	18.2
Diabetes	16.7	0	8.6	13.6	14.7	12.1
Clinical Outcome						
# pts Qualified	6	8	18	9	33	32
% Cured and Improved	83.3	75.0	100	100	100	87.5
Bacteriological Outcome*						
# Isolates Qualified	3	5	9	6	79	102
% Eradicated	3/3	4/5	88.9	100	98.7	73.5

*Uncorrected applicant's analysis in the original submission

b) Study No. CAZ-S10 Harlan Stone, M.D., Professor of Surgery, Emory University School of Medicine, Atlanta, Georgia, conducted a randomized controlled trial of ceftazidime and a regimen of tobramycin and clindamycin in the treatment of surgical infections. Hospitalized patients 12 years of age and older with deep and necrotizing skin and skin structure infections, or peritonitis were assigned to treatment groups to receive

Ceftazidime - 2.0 g q 8 h IV for 5-10 days, or
Tobramycin - 1.5 mg/kg q 8 h IV plus
Clindamycin - 600 mg IV q 6 h for 5-10 days.

Instead of a random code, as was used for other controlled studies in this application, the antibiotic used was determined by the last digit in previously assigned hospital numbers, odd numbers for ceftazidime and even numbers for the control.

Pretreatment cultures were obtained from the site of the infection within 24 hours of the initiation of treatment. Cultures were repeated during and after treatment whenever possible.

Most patients that were disqualified were disqualified because of surgical intervention which interferred with the evaluation of outcome.

The table, above, includes information for Dr. Stone's study. Results are shown below.

Intra-Abdominal Infections

	Stone (S10)				Gonzenbach (M50) (Applicant)	
	Applicant		Medical Officer			
	CAZ	TOB/CL	CAZ	TOB/Cl	CAZ	TOB/Cl
Clinical Response						
No pts. Qualified	18	9	18	9	33	32
Cures/DX						
Empyema of Gall Bl.	-	-	-	-	6	
Cholecystitis	-	2	-	2		
Peritonitis	8	4	8	4	15	11
Gangrenous bowel	1	-	1	-		
Intra-abd. abscess	3	1	3	1		
Diverticulitis	1	-	1	-		
Peri-appendiceal Absc.	-	-	-	-	4	3
Subphrenic Abscess	1	-	1	-	-	-
Abscess of Perforated Colon	-	-	-	-	-	1
Total Cured (%)	14	7	14	7	25	15
% Cured	77.8%	77.8%	77.8%	77.8%	75.8%	46.9%

Intra-Abdominal Infections Continued

	Stone (S10)				Gonzenbach (M50) (Applicant)	
	Applicant		Medical Officer			
	CAZ	TOB/Cl	CAZ	TOB/Cl	CAZ	TOB/Cl
Bacteriological Response*						
E. coli	1/1	1/1	1/1	1/1	15/15	7/7
Klebsiella species	-	1/1	-	1/1	3/3	2/5
P. mirabilis	-	-	-	-	1/2	1/3
Proteus species	-	-	-	-	-	1/2
Enterobacter species	-	-	-	-	3/3	-
Citrobacter species	1/1	-	1/1	-	1/1	1/1
Serratia species	-	-	-	-	1/1	-
H. influenzae	-	-	-	-	-	1/1
P. aeruginosa	-	1/1	-	-	-	2/2
S. aureus	1/1	-	1/1	-	6/6	2/2
B. fragilis					12/12	16/17
Bacteroides (not fragilis)	1/1	1/1	-	-	13/13	13/13
Clostridium species	-	1/1	-	-	6/6	7/7
Peptostreptococcus sp.	-		-	-	4/4	7/8
Peptococcus species	-	1/1	-	-	1/1	-
Bifidobacterium	-	-	-	-	-	1/1
Fusobacterium	1/1	-	-	-	-	1/1
Veillonella	2/2	-	-	-		
S. intermedius	1/1	-	-	-	-	1/1
Candida albicans	-	-	-	-	1/1	1/1
Pseudomonas species	-	-	-	-	-	1/1
S. pneumoniae	-	-	-	-	-	2/2
b. hemo strep	-	-	-	-	1/1	-
Streptococcus species	-	-	-	-	-	1/1
S. faecalis	-	-	-	-	8/8	4/7
Enterococci	-	-	-	-	2/2	1/1
S. Epidermidis	-	-	-	-	-	1/1
Total Eradicated	8	6	3	2	78	75
Total Qualified	9	6	3	2	79	102
% Eradicated	88.9	100%	(3/3)	2/2	98.7%	73.5%

* Number of qualified isolates eradicated/Number of qualified isolates

The applicant concludes that the results suggest that ceftazidime is as effective clinically as a regimen of tobramycin plus clindamycin in the treatment of intra-abdominal infections.

Reviewer's Comments: In the original submission, the medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Stone	#0310-008	Fusobacterium	Cure	p 19-048
Stone	#0310-008	Eubacterium	Failure	p 19-048
Stone	#0310-012	Veillonella	Cure	p 19-049
Stone	#0310-021	Bacteroides (not f)	Cure	p 19-050
Stone	#0310-021	S. intermedius	Cure	p 19-050
Stone	#0310-021	Veillonella	Cure	p 19-052

Tobramycin/Clindamycin

Stone	#0310-039	S. aureus	Cure	p 19-055
Stone	#0310-062	P. aeruginosa	Cure	p 19-056
Stone	#0310-062	Bacteroides (not f)	Cure	p 19-056
Stone	#0310-062	Clostridium sp.	Cure	p 19-056
Stone	#0310-062	Peptococcus	Cure	p 19-056

c) Study No. CAZ-M50 Hans R. Gonzenbach, M.D., member of the surgical staff at Kantonsspital of S. Gallen, Switzerland, conducted a randomized controlled trial of ceftazidime and a regimen of tobramycin and clindamycin in the treatment of serious intra-abdominal infections. Hospitalized patients 16 years of age and over were randomly assigned to two treatment groups to receive

Ceftazidime 2.0 g q 8 h IV for 7-10 days, or
Tobramycin 60-80 mg tid IV for 7-10 days plus
Clindamycin 600 mg tid IV.

The administration of other antibiotics normally required patients to be excluded from the study except where there was a suspicion of anaerobic bacterial infection after beginning treatment. In this instance metronidazole 500 mg tid IV was given.

Only patients whose infection was confirmed at the time of the operative procedure were considered evaluable. In this study susceptibilities of anaerobes as well as aerobes were tested.

The table, above, gives information for Dr. Gonzenbach's study. Results are shown directly above in the table with the results of Dr. Stone's study.

The applicant concludes that the efficacy data indicate that ceftazidime was superior to the control regimen. The bacteriological eradication rate was 98.7% for ceftazidime and 73.5% for the tobramycin/clindamycin regimen. Most failures in the contr l group were with E. coli isolates.

Reviewer's Comments

1. From a study of case reports in this study, the diagnoses were made at the time of the operative procedure and the condition was directly

relieved by the surgical procedure. Antibiotics were started in the operating room. Therefore, the response for all patients is due to both the surgical procedure, which relieved the cause of the illness, and to the antibiotic therapy and is most surely due more to the mechanical removal of the pathogenic organism than to the antibiotic. It is not clear whether the antibiotic use was therapeutic or prophylactic use. It is difficult to know what part of the patient's response should be attributed to the antibiotic, the surgery, or to the host's natural defenses.

2. In response to the reviewer's request, the applicant revised the bacteriological analysis of the last three studies, Drs. Brass, Stone, and Gonzenbach, to disqualify cases for which there had been no susceptibility testing. Bacteriological outcome was reported as follows

	Ceftazidime*	Tobramycin/Clindamycin*
E. coli	17/17	10/26
Klebsiella species	5/5	4/7
Proteus species	1/2	2/5
Enterobacter species	3/3	1/2
Citrobacter species	2/2	1/1
Pseudomonas species		3/3
S. faecalis	8/8	3/4
S. aureus	7/7	1/1
B. fragilis	12/12	16/17
Bacteroides (not frag.)	13/13	13/13
Clostridium species	6/6	7/7
Peptostreptococcus sp.	4/4	7/8
Other	5/5	6/6
Number eradicated	83	74
Number qualified	84	100
%	98.8%	74.3%

*Number of qualified isolates eradicated/Number of qualified isolates.

7. Urinary Tract Infections

a) Study No. CA7-U05 A randomized, controlled, multiclinic trial to compare ceftazidime and tobramycin in the treatment of complicated urinary tract infections was conducted at five clinical centers. Hospitalized adult patients were randomly assigned to two groups to receive either

Ceftazidime - 0.5 g IM q 12 h for 5-10 days, or
Tobramycin - 1.0 mg/kg/day IM q 8 h for 5-10 days.

FDA's Anti-Infective Drugs Advisory Committee's guidelines for the study of urinary tract infections were followed. The presence of the infection must be confirmed by urine cultures showing a concentration of the uropathogen of 100,000 or more per milliliter when obtained by the clean voided method, or

5000 or more per milliliter when obtained by suprapubic aspiration. This pretreatment urine specimen must be collected within 48 hours of the initiation of treatment. The uropathogen must be shown to be susceptible to the test drug and the control. Urine cultures must be repeated within 2-4 days after the initiation of treatment and again 5-9 days after treatment ends. Evaluation of outcome is based upon these cultures. Cultures obtained at 4-6 weeks after treatment ends to observe for relapses and re-infections are optional. The latter are felt to be host-related instead of drug-related.

Exclusions were the same as those given above.

The five investigators are listed below:

Clair Edward Cox II, M.D., Professor and Chairman of the Department of Urology, College of Medicine, University of Tennessee Center for Health Sciences, Memphis, TN,

Paul O. Madsen, M.D., Chief of Urology Service, Veterans Administration Hospital, Madison, WI,

Stacy J. Childs, M.D., Southeastern Research Foundation, Inc., Birmingham, AL,

Ronald David Miller, M.D., Director, Section of OB-GYN Infectious Diseases, Un. of California Irvine Medical Center, Orange, CA, and

Howard D. Solomon, M.D., Staff, Quadalupe Valley Hospital, Sequin, TX.

Four Urinary Tract Infection Studies

	Cox		Madsen		CAZ-U05 Childs		Miller		Solomon		CAZ-U07 Montgomerie		Prehein		CAZ-U09 Pittmann		CAZ-UTI Spitzy	
	CAZ	TOB	CAZ	TOB	CAZ	TOB	CAZ	TOB	CAZ	TOB	CAZ	MOX	CAZ	MOX	CAZ	TOB	CAZ	NET
Total	33	29	26	25	35	36	1	-	1	-	5	2	5	4	8	8	18	16
Age Under 18	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18-25	6	2	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-
26-35	-	4	1	-	3	3	1	-	1	-	2	2	-	-	-	-	-	3
36-50	7	5	1	1	2	3	-	-	-	-	-	-	-	-	-	-	3	-
51-65	20	17	13	13	8	5	-	-	-	-	-	-	2	2	1	1	2	3
Over 65	-	-	11	11	22	25	-	-	-	-	-	-	3	2	7	7	13	10
Mean	65.7	64.3	7.0	66.6	67.7	66.9	29	-	29	-	24.4	29.5	72.8	72.5	72.3	76.3	66.3	62.1
Sex M	24	25	26	25	13	14	0	-	1	-	5	2	3	4	5	6	14	11
F	9	4	-	-	22	22	1	-	-	-	-	-	1	0	3	2	4	5
Mean Duration (Days)	8.0	8.7	7.2	7.4	7.7	7.0	7.0	-	7	-	5.2	5.5	7.4	7.5	7.5	7.0	10	10
Concurrent Disorders																		
Neoplasia	3.0	20.7	42.3	24.0	25.7	16.7	-	-	-	-	-	-	20.0	25.0	12.5	12.5	16.7	25.0
Diabetes	15.2	6.9	15.4	24.0	0	2.8	-	-	-	-	-	-	40.0	25.0	12.5	12.5	5.6	6.3
Clinical Outcome																		
# pts Qual.	15	18	15	10	29	25	-	-	-	-	0	0	5	4	5	3	8	7
% Cured	100	100	100	100	100	88	-	-	-	-	-		100	4/4	5/5	3/3	100	71.4
Bacterio-logical Outcome*																		
# Isolates Qualified	22	20	17	12	37	30	-	-	-	-	4		4	3	8	6	17	15
% Eradicated	95.5	90.0	76.5	91.7	83.8	90.0	-	-	-	-	4/4	-	3/4	1/3	6/8	4/8	70.6	53.3

* Uncorrected applicant analysis in the original submission.

Urinary Tract Infections (CAZ-U05)-Outcome

	CAZ	TOB
Clinical Response		
No pts qualified	67	55
Cures /DX		
Cystitis	20	17
Unspec. UTI	21	14
Pyelonephritis	10	7
Prostatitis	-	0/?
Total cured (%)	51 (76.1%)	39 (70.9%)
Cured & Improved (%)	67 (100%)	52 (94.5%)
Bacteriological Response*		
E. coli	12/14	13/14
Klebsiella species	10/10	5/5
P. mirabilis	6/7	4/5
P. aeruginosa	17/23	22/24
Pseudomonas species	4/4	4/4
Proteus species	1/1	-
Enterobacter species	1/1	4/4
Citrobacter species	1/1	1/1
Serratia species	1/1	0/1
Other	5/6	3/3
Total Eradicated	58	55
Total Qualified	68	60
% Eradicated	85.3%	91.7%

*Number of qualified isolates eradicated/Number of qualified isolates.

The applicant concludes that the results of this multicenter trial indicate that ceftazidime is as effective as tobramycin in the treatment of complicated urinary tract infections due to E. coli, Klebsiella species, and Proteus mirabilis. Results suggest that ceftazidime is effective in eradicating Pseudomonas aeruginosa.

Reviewer's Comments

1. In the review of the original submission, the medical officer disqualified the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Childs	#0104-025	E. coli	Cure	p 19-305
Childs	#0104-054	P. aeruginosa	Failure	p 19-306

2. Once the applicant disqualified the above cases, the medical officer's analysis was essentially the same as the applicant's analysis. The difference in bacteriological cure rates was not statistically significant

b) Study No. CAZ-U07 A randomized, controlled, multiclinic trial to compare ceftazidime and moxalactam in the treatment of complicated urinary tract infections was conducted at two clinical centers. Hospitalized adult patients were randomly assigned to the following two groups:

Ceftazidime - 0.5 g IV q 12 h for at least 5 days, or
Moxalactam - 0.5 g IV q 12 h for at least 5 days.

Except for the difference in route of administration and control antibiotic, this study was the same as Study No. CAZ-U05, above.

Investigators were

John Zinzan Montgomerie, M.D., Chief of the Infectious Disease Division, Rancho Los Amigos Hospital, Downey, CA, and

Laurel C. Preheim, M.D., Chief of the Infectious Disease Section, Veterans Administration Medical Center, Omaha, NE.

Information about the populations in this study is shown in the urinary tract infection table, above.

Dr. Montgomerie treated seven patients for asymptomatic urinary tract infections. All had neurogenic bladders. All were unevaluable clinically because they were asymptomatic. Microbiological outcome is shown below.

	CAZ	MOX
Klebsiella species	2/2	0/1
P. mirabilis	1/1	-
Serratia species	1/1	-
Providencia species	1/1	-
E. coli	1/2	-
Citrobacter species	1/1	-
P. aeruginosa	-	0/1
Enterobacter species	-	0/1
Total qualified	7/8	1/3
% Eradicated	87.5%	

No efficacy conclusion can be drawn from the limited number of cases in this study.

c) Study No. CAZ-U09 A randomized controlled trial of ceftazidime and tobramycin in the treatment of complicated urinary tract infections was conducted by Walter Gay Pittman, M.D., a urologist at Lloyd Noland Hospital in Fairfield, Alabama. Hospitalized adult patients were randomly assigned to two groups to receive

Ceftazidime - 1.0 g IV q 12 h for 5-10 days, or
Tobramycin 1.0 mg/kg IV q 8 h for 5-10 days.

This study was similar to those described above. Seventy-five percent of this population had cardiovascular disorders. Population information is given in the table above.

Bacteriological outcome is shown below.

	Ceftazidime	Tobramycin
Klebsiella species	2/2	2/4
P. mirabilis	2/2	1/1
Proteus species	1/1	-
P. aeruginosa	1/3	1/3
Total	6/8	4/8
% Eradicated	75%	50%

Medical Officer's Comment: One ceftazidime-treated P. mirabilis cystitis case (No. 0314-012) should be disqualified because susceptibility testing was not reported.

d) Study No. CAZ-U11 Karl-Hermann Spitzy, M.D., Director of Chemotherapy at the University of Vienna, Vienna, Austria, conducted a randomized controlled trial of ceftazidime and netilmicin in the treatment of urinary tract infections due to Pseudomonas aeruginosa. Hospitalized patients 12 years of age or older were randomly assigned to two treatment groups for dosing as follows:

Ceftazidime - 1.0 g IV bid for 10 days, or
Netilmicin - 100 mg IV bid for 10 days.

The study was similar to those described above. Population information is given in the table above. Complicated infections were reported for 29 cases and uncomplicated infections were reported for five of the 34 cases.

	Applicant		Medical Officer	
	Ceftaz.	Netil.	Ceftaz.	Netil.
Clinical Response				
Cured or Improved				
Complicated UTI	8/8	3/5		
Uncomplicated UTI	-	2/2		
Bacteriological Response				
P. aeruginosa strains eradicated	12	8	0	0
P. aeruginosa strains qualified	17	15	0	0
% Eradicated	70.5%	53.3%		

From these controlled clinical trials, the applicant concludes that ceftazidime is as effective as its control in the treatment of urinary tract

infections caused by E. coli, Klebsiella species, Pseudomonas aeruginosa, and Proteus mirabilis.

> Medical Officer's Comment: All of Dr. Spitzer's cases are disqualified from the bacteriological evaluation by the medical officer since none have reports of susceptibility testing.

8. Bone and Joint Infections

Study No. CAZ-B03 The following four investigators participated in a multicenter study to evaluate the safety and efficacy of ceftazidime and a regimen of tobramycin and ticarcillin in the treatment of bone and joint infections in 20 patients:

Layne O. Gentry, M.D., Director, Infectious Disease Laboratory, Ben Taub General Hospital, Houston, TX.

Sheldon M. Markowitz, M.D., Assistant Professor of Medicine, Division of Infectious Diseases, Medical College of Virginia, Richmond, VA.

Jon Terry Mader, M.D., Assistant Professor, Department of Internal Medicine, Division of Infectious Diseases, The University of Texas Medical Branch, Galveston, TX.

Stephen Russell Zellner, M.D., Internist, Fort Meyers, FL.

At each clinic, hospitalized adult patients with acute osteomyelitis were randomly assigned to two treatment groups to receive

Ceftazidime - 2.0 g IV q 12 h for a minimum of 14 days, or
Tobramycin - 1.0 mg/kg q 8 h IV plus
Ticarcillin - 3.0 g IV q 4 h for a minimum of 14 days.

A positive pretreatment culture with an organism susceptible to the test drug was required. The culture was obtained by aseptic aspiration. A pre-treatment X-ray or radioisotopic scan of the affected area was required. Patient exclusions and the pretreatment screening evaluations were the same as those for other studies.

Clinical outcome was assessed as cured, improved or failure. Microbiological outcome was assessed as cure, failure, cure with superinfection, or failure with superinfection.

Bone and Joint Infections (CAZ-B03)

	Gentry		Markowitz		Mader		Zellner	
	CAZ	TNT	CAZ	TNT	CAZ	TNT	CAZ	TNT
Total	5	2	3	2	2	3	2	-
Age(yrs)								
Under 18	-	-	-	-	-	-	-	-
18-15	3	-	2	-	-	-	-	-
26-35	1	-	-	1	1	2	1	
36-50	-	1	1	1	1	-	1	
51-65	1	1	-	-	-	1	1	
Over 65	-		-	-	-	-		
Mean	33.2	51.5	25.7	36.0	37.5	42.3	54.0	-
Sex M	4	0	3	1	2	3	1	
F	1	2	0	1	0	0	1	
Mean Duration (Days)	42.4	38.5	25.0	30.5	44.5	52.3	16.5	
Clinical Outcome*	5 5/5	2 2/2	2 2/2	2 2/2	2 2/2	3 3/3	2 2/2	-
Bacteriological Outcome								
No. Isolates Qualified	6	3	4	1	2	3	1	-
% Eradicated	6/6	3/3	3/4	1/1	2/2	3/3	1/1	

*No. pts cured or improved/No. pts qualified

Bone and Joint Infections

Bacteriological Response*	Ceftazidime	Tobramycin/Ticarcillin
E. coli		1/1
P. mirabilis	2/2	
Enterobacter species	1/2	
Citrobacter species	1/1	
Serratia species	2/2	
P. aeruginosa	5/5	5/5
S. aureus	1/1	
Other		1/1
Total	12/13	7/7
% Eradicated	92.3%	100%

*Number of pathogens eradicated/No. of pathogens qualified

The applicant concludes that the limited data from these controlled trials suggest that ceftazidime is as effective as the tobramycin/ticarcillin regimen.

9. Serious Gram-Negative Infections

Study No. CAZ-A03 - A double-blind randomized controlled multiclinic trial to compare ceftazidime and moxalactam in the treatment of serious gram-negative infections was conducted at five clinical centers. Antibiotic regimens used to treat these infections have usually included aminoglycosides. The extended spectra of moxalactam and ceftazidime indicate that they may be used singly.

Hospitalized patients 12 years of age and over suspected of having a serious infection due to aerobic gram-negative micro-organisms were selected to receive either

Drug A - Ceftazidime - 2.0 g IV q 8 h for approximately 7 days, or
Drug B - Moxalactam - 2.0 g IV q 8 h for approximately 7 days.

The monitor at the University of Maryland was the only individual to have the identities of Drug A and Drug B. Drugs were delivered to hospital pharmacies as either Drug A or Drug B and were dispensed using sealed envelops according to a random code.

Diagnoses were confirmed by culture and susceptibility testing of specimens from appropriate sites and by consistent symptoms, signs, and X-ray.

Investigators were

John Windiate Warren, M.D., Assistant Professor of Medicine, Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, MD,

William C. Anthony, M.D., Internal Medicine, Baltimore, MD,

Harold C. Standiford, M.D., Head, Section of Infectious Diseases, Veterans Administration Medical Center, Baltimore, MD,

John P. Manzella, M.D., Division of Infectious Diseases, York Hospital, York, PA, and

Ronald Wayne Geckler, M.D., Chief of the Division of Infectious Diseases, Mercy Hsopital, Inc., Baltimore, MD.

Serious Gram-Negative Infections (CAZ-A03)

	Warren		Anthony		Standford		Manzella		Geckler	
	CAZ	MOX	CAZ	MOX	CAZ	MOX	CAZ	MOX	CAZ	MOX
Total	27	26	8	5	2	2	3	4	2	2
Age (yrs)										
Under 18	-	1	-	-	-	-	-	-	-	-
18-25	7	6	2	-	-	-	1	-	-	-
26-35	6	9	1	-	1	-	1	-	-	-
36-50	6	3	2	1	-	-	-	1	-	-
51-65	4	2	-	-	-	-	1	-	-	1
Over 65	4	5	3	4	1	2	-	3	2	1
Mean	41.4	40.0	49.4	75.0	49.0	86.0	38.3	70.3	77.0	66.0
Sex M	16	17	5	2	2	2	2	4	0	2
F	11	9	3	3	0	0	1	0	2	0
Mean Duration (Days)	7.5	7.3	9.5	9.4	11.5	6.0	10.0	11.0	9.5	9.5
Concurrent Disorders %										
Diabetes	14.8	11.5	0	20	-	-	33.0	0		
Alcoholism	14.8	7.7	0	0	-	-	0	0		

All four of Dr. Standiford's cases were disqualified from the microbiological evaluation, three because of inadequate follow-up cultures and one because the patient expired.

The applicant did not summarize the efficacy data in this study.

Reviewer's Comments:

1. The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Moxalactam

Warren	#0234-008	E. coli	Cure	p 20-264
Warren	#0234-008	Acinetobacter sp.	Cure	p 20-264
Warren	#0234-032	P. aeruginosa	Cure	p 20-265
Warren	#0234-052	Klebsiella sp.	Cure	p 20-266
Manzella	#0239-005	P. mirabilis	Cure	p 20-309
Manzella	#0239-005	Enterobacter sp	Cure	p 20-309

2. The reviewer tallied and summarized the data from the five investigators in this study as follows:

Antibiotic Form 50-578

MEDICAL OFFICER'S REVIEW OF LABELING
and MEMORANDA OF TELEPHONE CONVERSATIONS and CONFERENCE
Original Labeling
and Labeling Revisions Dated June 8, Sept. 21, and Dec. 11 and 14, 1984

Applicant: Glaxo, Inc.

Name of Drug: Generic: Ceftazidime for Injection (Ceftazidime pentahydrate)

Trade: FORTAZ™

Telephone Conference December 11, 1984: I called M. David MacFarland, Ph.D., Director of Regulatory Affairs at Glaxo to discuss ceftazidime labeling. We felt that if there were no major controversies about labeling, our labeling discussions could be held over the telephone. He put the call on a speaker phone so that Dr. James Chubb and Dr. Andrew Finn at Glaxo could join the conversation. We discussed the Indications and Usage section and I gave them the following claims which are felt to be acceptable:

1. Lower Respiratory Tract Infections, including pneumonia due to

Pseudomonas aeruginosa	E. coli
H. influenzae	Serratia species
Klebsiella species	Citrobacter species
Enterobacter species	S. pneumoniae
P. mirabilis	S. aureus (methicillin-susceptible strains)

2. Skin and Skin Structure Infections due to

P. aeruginosa	Citrobacter species
Klebsiella species	Serratia species
E. coli	S. aureus (methicillin-susceptible strains)
Enterobacter species	S. pyogenes (Group A beta hemolytic streptococci)
Proteus species	
P. mirabilis	

3. Urinary Tract Infections due to

Pseudomonas aeruginosa	Klebsiella species
Other Pseudomonas species	Serratia species
Enterobacter species	E. coli
Proteus species	P. mirabilis

4. Bacterial Septicemia due to

Pseudomonas aeruginosa	Enterobacter species
Klebsiella species	Serratia species
H. influenzae	S. pneumoniae
E. coli	S. aureus (methicillin-susceptible strains)
P. mirabilis	S. epidermidis (methicillin-susceptible strains)

5. Bone and Joint Infections due to

Pseudomonas aeruginosa
Klebsiella species
Proteus species
Serratia species
Enterobacter species
S. aureus (methicillin-susceptible strains)

6. Gynecological Infections including endometritis, pelvic cellulitis, and other infections of the female genital tract due to

E. coli
beta hemolytic streptococci
Klebsiella species
S. aureus (methicillin-susceptible strains)

7. Intra-abdominal Infections including peritonitis due to

Pseudomonas aeruginosa
E. coli
Klebsiella species
Enterobacter species
S. aureus (methicillin-susceptible strains)

8. Central Nervous System Infections including meningitis due to

Pseudomonas aeruginosa
H. influenzae
N. meningitidis
S. pneumoniae

The following claims are not supported and are deleted from the Indications section:

1. Lower Respiratory Tract Infections - Delete Acinetobacter species and other Pseudomonas species.

2. Skin and Skin Structure Infections - Delete other Pseudomonas species, Acinetobacter species, S. epidermidis, and polymicrobial infections caused by aerobic and anaerobic organisms including Peptococcus species, Peptostreptococcus species, and Bacteroides species.

3. Urinary Tract Infections - Delete Providencia species.

4. Bacterial Septicemia - Delete other Pseudomonas species and Salmonella species.

5. Bone and Joint Infections - Delete other Pseudomonas species and S. epidermidis.

6. Intra-abdominal Infections - Delete Clostridium species.

7. Central Nervous System Infections - Delete Salmonella species.

Deleted micro-organisms which are not mentioned elsewhere in the section should appear in the Microbiology section with an indication of

microbiological activity but with a statement that the clinical significance is unknown.

Glaxo representatives had no objections to these revisions. I told them that our microbiologist, Dr. James King would discuss the Microbiology section with them. I said I would talk to them again about adding Bacteroides species under gynecological and intra-abdominal infections subheadings.

In-House Conference with Drug Advertising: Glaxo's proposed labeling, dated September 21, 1984, as revised by the medical officer and other members of the review team, was reviewed by Mr. Kenneth Feather, Drug Advertising Regulation Branch and found to be acceptable.

Amendment Dated Dec. 11, 1984: The applicant files a revised Table 2 for page 3 of the proposed labeling. This table which gives tissue and fluid concentrations for ceftazidime, has been revised to add a column for the number of patients and a column giving the time the samples were collected.

Telephone Conference December 12, 1984: I called Glaxo and a similar conference was held to discuss all the other sections of the proposed labeling. We reviewed each section of the insert and made many minor editorial changes. Sentences were revised and some were transferred to other places.

I recommended that the phrase "...which was discovered and developed by Glaxo Group Research" in the Description section be deleted. This phrase may be used in ceftazidime advertising but it is not appropriate for the chemical identity section.

I have reviewed the Bacteroides case reports again and have looked at the in vitro data with the microbiologist. We recommended that the following lines be added to the Indications Section under the subheadings Gynecological Infections and Intra-Abdominal Infections:

> "...and polymicrobial infections caused by aerobic and anaerobic organisms, including Peptococcus species, Peptostreptococcus species and Bacteroides species (Many strains of B. fragilis are resistant.)"

In keeping with a recommendation from the pharmacologist, rabbits were deleted from the usage in pregnancy paragraph. Embryotoxicity had been encountered at all doses (25-200 mg/kg).

The two tables that give dosage recommendations, Tables 3 and 4, were combined to make one table. This table will have a footnote which will read,

> "Although clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis."

There were no controversial changes. Dr. McFarlane said that he would send the revised version to the United Kingdom for review. He felt that he would be able to file revised proposed labeling by Dec. 17, 1984. When he suggested preparing a rough printing, I cautioned him about printing it too soon. Proposed labeling could be revised again anytime before the action letter

issues. If it is printed too soon, it would have to be done over if new changes were found to be necessary.

Telephone Conversation December 14, 1984: Dr. MacFarland called to ask again about the Description section phrase "...which was discovered and developed by Glaxo Group Research." His marketing people want very much to retain this phrase. Glaxo agreed with everything else that had been discussed.

I replied that all those at FDA who have reviewed the proposed labeling so far, and that includes our Division of Drug Advertising, agree that that phrase is not appropriate. We do not recommend that it be used. When he asked if we could reconsider this, I replied that if Glaxo wants to leave it in, he can always file revised labeling retaining this phrase. However, when it is reviewed on the office level, a request to remove it will probably be put in the action letter if the office agrees with us that it is not appropriate. There is a chance that they will leave it in but, in my view, it is very slim.

Amendment Dated December 14, 1984: The applicant files labeling which has been revised in an attempt to comply with our labeling conferences with the firm. My comments on the new version are listed below:

1. Although we recommended that the phrase in the Description section, "....which was discovered by Glaxo Group Research," be deleted, Glaxo, at my suggestion, has elected to retain it for judgement by others who will review the proposed package insert before the action letter issues.

2. A minor editorial comment which will be corrected by printing, is that everywhere a bacterium is named in a typewritten manuscript the two words in the name should be underlined separately. In other words, the lines under the genus name and species names should be separated by the space between the two parts of the name. This will be corrected with italicized print. Similarly, when "in vitro" is typewritten the words are underlined separately. I counted 64 places in the proposed labeling where the underlining should be broken.

3. There should be a hyphen in "30-mcg" in the phrase "30-mcg ceftazidime disk" in two places on page 7 under the Susceptibility Tests subheading.

4. The word "species" after the name Klebsiella should be spelled out under the subheading Lower Respiratory Tract Infections in the Indications and Usage section on page 8.

5. The word "and" should be inserted before "S. pyogenes (group A beta hemolytic streptococci" on page 8 under the subheading Skin and Skin Structure Infections in the Indications and Usage section.

6. In the Indications and Usage section on page 10, the paragraph which begins, "Therapy may be instituted before results...," should not be a separate paragraph, but should be a continuation of the previous paragraph.

7. The last sentence on page 12 under the subheading Drug Interactions should be revised to read, "Nephrotoxicity and ototoxicity were not noted when FORTAZ was given alone in clinical trials." This deletes the phrase "To date," a

phrase that would require continuous updating of the labeling to keep up with drug experence reports.

8. In the Dosage and Administration Section, the word "However" at the beginning of the last sentence on page 14, should be deleted.

Amendment Dec. 19, 1984: I called Dr. MacFarlane to give him the comments which are listed above on the Dec. 14 labeling. All comments were accepted except that Glaxo wants to retain the phrase in the Description section. Revised proposed labeling will be submitted today.

Recommendations: This application should be considered approvable pending receipt of satisfatory labeling. There is full agreement on the proposed labeling except that Glaxo is firm in its wish to retain the Description section phrase "...which was discovered and developed by Glaxo Group Research." The medical officer recommends that the Agency's decision about this phrase be included in the action letter on this application.

Theresa Greene Reed

Theresa Greene Reed, M.D., M.P.H.

cc
Orig Form 50-578 2/14/85
HFN-815 ST
HFN-815/Reed
HFN-815/Rhinehart
HFN-815/Norton
HFN-340/Kelsey
HFN-235
2094b

January 18 and 31, 1985

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF FORM 50-578

Applicant: Glaxo, Inc.
Research Triangle Park, NC

Name of Drug: Ceftazidime for Injection

Three short conferences with the Group Leader and the Division Director have been held as part of the review of the MOR dated December 14, 1984. Ceftazidime micro-organisms were evaluated in the same way that micro-organisms in all of my previous reviews were evaluated.

As in my previous Form 5 reviews, acceptable randomized controlled trials are required for specific indications and the data from these trials must be adequate to support the claims, that is, the test drug's eradication rates must be equal to or better than eradication rates for the control drug. However, as in the past, micro-organisms at these anatomic sites are handled in an entirely different manner. There is much more leeway with micro-organisms than there is with anatomic sites. Micro-organisms are accepted for each claim, not only on the basis of the number of pathogens eradicated at the site, but also on the basis of a medical judgement for each pathogen at that site. Factors which play a part in these medical judgements are

1. The type of infection and the ease with which controlled trials can be conducted (controlled trials for some conditions can't be conducted),

2. The estimated incidence of the infection, rare infections requiring fewer organisms than common infections,

3. The ability of the antibiotic to diffuse into the site and to maintain therapeutic concentrations,

4. The reported mean inhibitory concentration of the pathogen, and

5. The total eradication rate at all sites for the specific pathogen, large numbers at one site being very supportive of small numbers at another site when there is good diffusion into that site.

This policy was explained on pages 5-6 of my memorandum dated July 14, 1983 to the Acting Director of New Drug Evaluation about cefuroxime, also a Glaxo antibiotic. (The Division of Anti-Infective Drug Products was a part of NDE at that time.) This memorandum was signed by the Division Director, at that time, on July 15, 1983. The section about this topic reads as follows:

"My recommendation for approval of individual indications is based upon mean cure rates for all organisms isolated in controlled trials for the major specific claims (e.g., 100% cefuroxime cure rate for all five species causing skin and skin structure infections compared with 91% cure rate for the control group. Glaxo's rates and the medical officer's rates are compared.

"Most of the time controlled trials cannot be conducted for such life-threatening infections as bacterial septicemia and meningitis. Glaxo's program was unique in that they conducted controlled trials for these life-threatening conditions.

"Recommendations regarding individual micro-organisms for each claim are handled differently. When the total number for a specific organism is satisfactory in a controlled trial at a specific anatomical site and its eradication rate is satisfactory for that site, that specific organism is approved at other sites where there are adequate supportive uncontrolled data but no controlled trial isolates, if in vitro susceptibility data support it and if the drug diffuses into the site. For example, Hemophilus influenzae had good numbers in controlled lower respiratory tract studies but none were found in controlled studies of septicemia. Since the uncontrolled H. influenzae septicemia cure rate was 8/8, then, H. influenzae is approved. Another example is S. aureus in bacterial septicemia. For S. aureus there was a 100% cure rate in controlled skin and skin structure trials and a 50% cure rate in controlled lower respiratory tract infections. These rates are supported by cure rates from all protocols for these infections of 141/150 and 15/16, respectively. Therefore, S. aureus is accepted under bacterial septicemia where there was a 22/22 cure rate even though S. aureus was not found in the controlled bacterial septicemia trial. Similar judgements are made based upon cure rates from both controlled and uncontrolled trials, in vitro susceptibility data both from the Form 5 and from quarterly computerized summaries of antibiotic susceptibilities in hospitals throughout the country (BAC-DATA), and data confirming diffusion of the antibiotic into the site and the maintenance of therapeutic levels at that site. In vitro susceptibility data, including global susceptibility patterns (resistance of the gonococcus in Southeast Asia) play a very important role in making these decisions. However, controlled trials must have been conducted for the anatomic site (except for certain catastrophic infections where historical control can be substituted)."

This policy has now changed and approval of micro-organisms is more rigorous than it has been in the past.

The medical officer's master tally of micro-organisms which was prepared to make decisions regarding pathogens for the package insert was not included in the December 14, 1984 MOR. It is shown below.

MASTER MICRO-ORGANISM TALLY SHEET

	Lower Resp I			Skin & St.I			Urin T Inf			Septicemia		Bone & Joint		Intra-Abd I		Gyn.		Meningitis		
	CONT		UNC	CONT		UNC	CONT		UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT		UNC
E. coli	*46 48	(44) (46)	6 6	*23 25		4 4	*104 111	(101) (108)	27 27	*17 17	13 13		1 1	*17 17	4 4	*11 11				
Klebsiella sp.[a]	*42 43	(41) (42)	15 16	*17 19		6 7	* 24 26		15 15	* 3 3	4 4	*	5 5	* 5 5	2 2	3 3				
P. mirabilis[b]	*23 24	(22) (23)	7 8	*30[c] 33		4 4	* 21[c] 23	(20) (22)	8 8	1 1	1 1	2 2	2 2			2 2				
Proteus sp.[d] Indole +	2 2			6[c] 7		1 1	4[c] 5		2 2			2 2	5 5							
Enterobacter spe	*23 26		3 5	*16 18		6 6	* 5 5		1 3	2 2	1 1	* 2 3	5 6	3 3						
Citrobacter sp.[f]	* 7 7		1 1	3 3		1 1	2 2				1 1	2 2								
H. influenzae	*27 27	(26) (26)	25 25							*10 10								*17 17	(14) (14)	2 2
Hemophilus sp.	3 3																	1 1		
S. pneumoniae	*38 39	(36) (37)	13 13							* 9 9								[e] 5 6	(4) (5)	
P. aeruginosa	*22 36		32 42	*39 42	(40) (43)		*38 56	(25) (38)	23 28	* 4 4	3 3	* 6 6	31 35	1 1	2 2			[e] 5[h] 5		
Pseudomonas sp.	* 79 7			X			4 4			X 1 1		X	1 1					3[h] 3		
S. aureus	*16 19		5 6	*61 74	(60) (73)	9 10				2 3		* 3 3	15 16	* 7 7		2 2				

Continued next page

MASTER MICRO-ORGANISM TALLY SHEET - Continued

	Lower Resp I		Skin & St.I		Urin T Inf		Septicemia		Bone & Joint		Intra-Abd I		Gyn.		Meningitis	
	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC
Acinetobacter sp.	1/1		X 3/3							1/1						
S. pyogenes	2/2		*32 1/32		7/7						1/1		6/6			
Beta hem. strep.	3/3		*19 1/20		2/2		2/2									
Enterococci	1/1															
Serratia sp.	* 4/4	6/6	* 1/1		5/5	2/2	2/3	* 5/5	4/4	2/2		3/3				
S. epidermidis			X					3/3	3/3	X						
Polymicrobial infections including			X								*					
Bacteroides sp. (not fragilis)											*13 13		19 (17) 21 (19)			
Peptostreptococcus											4/4	1/1	4/4			
Peptococcus sp.											X 1k 1		3/4			
Clostridium sp. (not difficile											6/6					
Salmonella sp.					X								X 2/2			
Providencia sp.					X 2/2											

Continued next page

MASTER MICRO-ORGANISM TALLY SHEET - Continued

	Lower Resp I		Skin & St.I		Urin T Inf		Septicemia		Bone & Joint		Intra-Abd I		Gyn.		Meningitis	
	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC	CONT	UNC
N. meningitidis[l]							1 1								* 8 (7) 8 (7)	
S. viridans							2 2									
S. faecalis[m]											8 8					
B. fragilis[m]											12 12					

CONT - Controlled trials UNC - Uncontrolled trials

( ) - Medical Officer's evaluation where it differs from the applicant's evaluation.

* - Recommended for proposed labeling.

d - Add sentence which reads, "Ceftazidime has also been used successfully in a limited number of cases of meningitis due to P. aeruginosa and S. pneumoniae."

a - The mean MIC for Klebsiella species = 0.3 mcg/ml.

b - The mean MIC for Proteus mirabilis = 0.02 mcg/ml, the lowest MIC for all pathogens tested.

c - The listing recommended for the Indications section reads "Proteus species including P. mirabilis and indole + Proteus."

d - The mean MIC for Proteus species = 0.07 mcg/ml.

e - The mean MIC for Enterobacter species = 0.4 mcg/ml.

f - The mean MIC for Citrobacter species = 0.2 mcg/ml.

g - LRI due to Pseudomonas species was originally deleted by the MO but should have been recommended for inclusion.

h - From the amendment dated November 21, 1984.

i - The listing recommended for the Indications section (and recommended by the microbiologists) is "S. pyogenes (group A beta hemolytic streptococci)."

j - The mean MIC for Serratia species = 0.1 mcg/ml.

k - The claim for Peptococcus species under intra-abdominal infections, originally recommended, is now deleted.

l - The MIC range for N. meningitidis = 0.03-0.12 mcg/ml. There is good penetration of the inflamed blood-brain barrier.

m - Since S. faecalis and some strains of B fragilis are resistant, more cases are needed.

My response to other concerns at these conferences are listed below:

1. The overall summary of adequate and well-controlled studies is given on page 106 of the December 14, 1984 MOR. This summary is now expanded to include the tally for pathogens shown above. More detail will be found with the summaries of individual studies.

2. The medical officer's conclusion is given on page 105 of the December 14 MOR. For each claim, as pointed out in the write-up, there was no statistically significant difference in favor of the various control antibiotics for any claim. Where there might have been a question, p values are given in the medical officer's comments, e.g., first two lines on page 39.

3. Ceftazidime has been proven in many more than two adequate and well-controlled trials to be both as safe and effective as the various control regimens. The following 15 randomized controlled trials were acceptable:

Lower respiratory tract infections and/or septicemia	4 multiclinic studies at 21 centers (R03, R04 & R07, and R08)
Skin and skin structure infections	3 multiclinic studies at 20 centers (S03, S04, S07)
Gynecological infections	1 multiclinic study at 2 centers (S09)
Intra-abdominal infections	3 multiclinic studies at 3 centers (S08, S10, and M50)
Urinary tract infections	1 multiclinic study at 5 centers (U05)
Bone and joint infections	1 multiclinic study at 4 centers (B03)
Serious gram-negative infections	1 multiclinic study at 5 centers (A03)
Central nervous system infections	1 multiclinic study at one center (M01)

These 14 acceptable randomized controlled trials (studies R04 and R07 are taken together) are supported by 15 other randomized controlled trials and 19 uncontrolled trials, many of which were multiclinical studies.

4. Ceftazidime is acceptably safe. The adverse reaction rate for ceftazidime, 6.2% given on page 91, when compared with the adverse reaction rates for the nine control regimens given on page 93 of the MOR, show comparative safety. These ceftazidime reactions were all minor and the incidence was 2% or less, as stated on page 91. These rates are acceptable.

5. In clinical trials ceftazidime was discontinued in 50 patients, 1.9%, because of minor experiences such as rash and diarrhea. Most of the 158

patients experiencing the 216 adverse reactions tolerated the reaction or the reaction itself disappeared during treatment. Unfortunately, the application does not have similar information for the nine control regimens.

(The adverse reactions listed on pages 102 through 105 are not clinical trials data. These are domestic and spontaneous international drug experience reports which were filed after the Form 5 was filed and which the applicant is required by law to file. They were included so that all amendments to the Form 5 would be reviewed.)

New changes for the proposed ceftazidime labeling and which will now be discussed with the applicant are listed below.

1. Add "Pseudomonas species" to the lower respiratory infection claim.

2. The following micro-organisms which were recommended in the MOR dated Dec. 14, 1984 are now deleted:

   a) Skin and Skin Structure Infections - Citrobacter species.

   b) Urinary Tract Infctions - Pseudomonas species and Serratia species.

   c) Bacterial Septicemia - P. mirabilis, Enterobacter species, S. aureus, and S. epidermidis.

   d) Bone and Joint Infections - Proteus species, including P. mirabilis, and Serratia species.

   e) Gynecological Infections - Klebsiella species, S. aureus, beta bemolytic streptococci, and polymicrobial infections caused by aerobic and anaerobic organisms, including Peptococcus species, Peptostreptococcus species, and Bacteroides species (many strains of B. fragilis are resistant).

   f) Intra-Abdominal Infections - P. aeruginosa, Enterobacter species, Peptococcus species, and Peptostreptoccus species.

   g) Central Nervous System Infections - P. aeruginosa and S. pneumoniae.

3. Under Skin and Skin Structure Infections and Urinary Tract Infections, "Proteus species, including P. mirabilis" should be revised to read "Proteus species, including P. mirabilis and indole-positive Proteus."

4. Add a sentence after the Central Nervous System Infection indication which reads, "Ceftazidime has also been used successfully in a limited number of cases of meningitis due to P. aeruginosa and S. pneumoniae."

Recommendation: Approval of the ceftazidime application is recommended. However, proposed labeling is unsatisfactory. Revised proposed labeling is being requested. (See Memorandum of TC Jan. 31, 1985.)

Theresa Greene Reed

Theresa Greene Reed, M.D., M.P.H.

cc
Orig Form 50-578
HFN-815 ET 2/4/85
HFN-815/Reed
HFN-815/Norton
HFN-235
2872b

Antibiotic Form 50-578 December 20, 1984

MEDICAL OFFICER'S REVIEW OF LABELING

Amendment Dated Dec. 19, 1984

Applicant: Glaxo, Inc.

Name of Drug: Generic: Ceftazidime for Injection (Ceftazidime pentahydrate)

Trade: FORTAZ™

Proposed labeling which was revised in keeping with our comments was submitted. There are two comments.

1. The phrase "...which was discovered and developed by Glaxo Group Research" should be deleted.

2. The verb in the last sentence on page 12, "have not been," should be changed to "were." The revised sentence will read, "Nephrotoxicity and ototoxicity were not noted when FORTAZ was given alone in clinical trials."

The Group Leader, Dr. Stanley, called Dr. MacFarlane, Glaxo's Director of Regulatory Affairs, to give him the first comment and I called him to give him the second comment. He replied that these changes will be made and he will submit another revision.

Recommendation: The application should be made approvable pending submission of satisfactory labeling.

Theresa Greene Reed

Theresa Greene Reed, M.D., M.P.H.

cc
Orig Form 50-578
HFN-815 CT 2/4/85
HFN-815/REed
HFN-815/Rhinehart
HFN-815/Norton
HFN-340/Kelsey
HFN-235
2611b

15279

Antibiotic Form 50-578 December 20, 1984

MEDICAL OFFICER S REVIEW OF LABELING

Amendment Dated Dec. 19, 1984

Applicant: Glaxo, Inc.

Name of Drug: Generic: Ceftazidime for Injection (Ceftazidime pentahydrate)

Trade: FORTAZ™

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Recommendation: The application should be made approvable pending submission of satisfactory labeling.

Therese Greene Reed

Therese Greene Reed, M.D., M.P.H.

cc
Orig Form 50-578
HFN-815
HFN-815/Reed
HFN-815/Rhinehart
HFN-815/Norton
HFN-340/Kelsey
HFN-235
2611b

February 8, 1985

MEDICAL OFFICER'S REVIEW OF ANTIBIOTIC FORM 50-578

Submissions dated Jan. 3, 8, 9, 16, 22, 25, 29, and 31, and Feb. 4 and 5, 1985

Applicant: Glaxo Incorporated
Research Triangle Park, NC

Name of Drug: Trade: FORTAZ®

Generic: Ceftazidime pentahydrate for injection

Amendments Dated Jan. 3, 8, 9, 10, 16, and 29, 1985: Drug experience reports from ongoing clinical trials are crossfiled from the IND to the Form 5.

Amendment Dated January 25, 1985: In response to a request by FDA's microbiologist, Dr. James King, Glaxo provides final NDA specifications and methods. All previously submitted revisions and amendments and agreements are compiled into a single document.

Amendment Dated January 31, 1985: In response to my request, revised pages 62-64 of the Sept. 5, 1984 amendment are filed. These pages include data from the uncontrolled bone and joint infection studies which had been omitted.

Amendment Dated February 4, 1985: In response to our request, revised labeling is filed. The applicant accepts our request to delete some pathogens and this version complies with the requests made in my telephone conversation with Dr. James Chubb of Glaxo on January 31, 1985 and contains all the changes listed on page 7 of my Jan. 18 and 31, 1985 amendment to my original MOR.

Medical Officer's Comment: This revised labeling is satisfactory.

Amendment Dated February 5, 1985: Glaxo is very interested in having "Bacteroides species" in the gynecological indication and in having "S. aureus (methicillin-susceptible strains)" in the bacterial septicemia indication. Therefore, a new revised package insert, identical to the submission dated February 4, 1985 but with these two additions, is filed. The submission contains a letter written to accentuate Glaxo's position regarding these two micro-organisms.

A. Bacteroides species

Data to support the claim for gynecological infections due to Bacteroides species was presented in the original Form 5 but "this data was not clearly placed in the proper clinical and bacteriological perspective in order to discuss the importance of this indication for ceftazidime." The original application contained a report of study No. CAZ-S09, a randomized controlled multicenter trial comparing ceftazidime with a regimen of tobramycin plus clindamycin. All but one of the 79 women who were enrolled were treated by Jorge D. Blanco, M.D., and his colleagues at the University of Texas Health Science Center in San Antonio. They were predominantly indigent, Mexican-American women in their 20's who were hospitalized with a diagnosis of endometritis, salpingitis, or pelvic cellulitis after hysterectomy. Cultures

were obtained from the infected site and from blood.

Of the 38 patients randomized to the ceftazidime group, 17 patients had symptomatic endometritis with a uterine specimen culture which was positive for a ceftazidime-susceptible strain of Bacteroides species as follows:

Bacteroides bivius	16
Bacteroides fragilis	2
Bacteroides capillosus	1

These isolates were single-organism isolates for three patients and polymicrobial isolates for 14 patients. All isolates were susceptible to ceftazidime except the enterococcus. Bacteriological and clinical cures occurred in 15 of the 17 patients. Two B. bivius strains persisted. The investigators report that B. bivius is a common genital pathogen.

A report of this study was published in 1983 (Randomized comparison of ceftazidime versus clindamycin-tobramycin in the treatment of obstetrical and gynecological infections. Blanco JD, Gibbs RS, Duff P, Castaneda S, and St. Clair PJ. Antimicrob Agents & Chemother 1983 Oct; 24 (4): 500-504).

Reviewer's Comment: A consultation with the Division Director was held to consider this micro-organism and the inclusion of this claim is not recommended. Although 15 of 17 qualified isolates were eradicated, only three were single-organism isolates. The remainder were polymicrobial isolates. Also, Bacteroides brevius, the most frequently isolated strain, is not a common pathogen.

B. Staphylococcus aureus

Data supporting ceftazidime in the treatment of bacterial septicemia due to Staphylococcus aureus (methicillin-susceptible strains) were reviewed by the applicant. Initial evidence was presented in the Form 5 and additional supportive data have become available from post-NDA clinical trials. This cumulative data complements the previously well-supported indications for ceftazidime in the treatment of lower respiratory tract infections, skin and skin structure infections, bone and joint infections, and intra-abdominal infections due to S. aureus.

S. aureus (methicillin-susceptible strains) was found in 288 of the pretreatment isolates from all patients in the Form 5. Only 16 (5.6%) were resistant to ceftazidime. Susceptibility testing of these 288 isolates was reported as follows:

Susceptible	78.3%
Intermediate susceptibility	16.1%
Resistant	5.6%

The current data base contains case reports for 25 patients with septicemia due to S. aureus who were treated in a variety of clinical studies. Fifteen were presented in the original submission and ten come from post-NDA clinical trials. Case reports for the ten new cases are submitted and all cases are summarized.

The applicant analyzed these 25 cases as follows:

Total number		25
Had at least two positive pretreatment blood cultures		21
Had only one positive pre-treatment blood culture		4
S. aureus susceptible to CAZ		19
S. aureus resistant to CAZ		1
No susceptibility test report		5
Evaluable cases with at least two pretreatment blood cultures		8
Evaluable cases with only one pretreatment blood culture		4
Total Evaluable cases		12
Bacteriological outcome		
Eradicated		10/12
Persisted		1/12
No follow-up culture		1/12
Clinical outcome		
Cured		9/12
Improved		1/12
Failed		2/12
Disqualified		10
Length of Rx too short	7	
Concurrent vancomycin	1	
Organism resistant	1	
No susceptibility data	1	

The applicant concludes that this information supports the use of ceftazidime in the treatment of septicemia due to S. aureus and complements data which have already been submitted to the Form 5 supporting treatment of other infections due to S. aureus given in the proposed labeling.

Medical Officer's Comments

1. The medical officer's analysis of these 25 cases which differs from the applicant's analysis is shown below:

	7 cases (7 isolates)
Qualified cases	
Bacteriological Cures	6/7
Clinical Cures	5/7
Clinical Improvement	1/7
Clinical Failure	1/7
Disqualified cases	
No follow-up culture	1
Only one positive pre-Rx culture	4
Insufficient length of Rx (1-day - 2 pts, 2-days - 3 pts)	5
Expired on day 2	1
Concurrent vancomycin Rx	1
No susceptibility data	5
Resistant organism	1

These disqualifications are not unexpected and the reasons for them are acceptable.

2. Although 18 cases must be disqualified, there remain seven acceptable S. aureus septicemia cases, four more than were in the original submission. Of these, six (85.7%) were bacteriological cures. This 6/7 cure rate is supported by an overall cure rate for other S. aureus cases in the Form 5 of 88.7% (118/133 isolates).

3. The inclusion of S. aureus septicemia is recommended.

Conclusion and Recommendations:

1. The reviewer recommends approval of this application with labeling that includes septicemia due to S. aureus (methicillin-susceptible strains). The inclusion of gynecological infections due to Bacteroides species is not recommended.

2. The approvable letter should indicate that revised proposed draft labeling which was filed February 5, 1985 is satisfactory except that it should be revised to delete Bacteroides species from the gynecological indication.

3. Final printed labeling should be requested.

Theresa Greene Reed

Theresa Greene Reed, M.D., M.P.H.

cc
Orig Form 50-578
HFN-815/Norton
HFN-815
HFN-235
HFN-815/Reed
3097b

Serious Gram-Negative Infections (CAZ-[illegible])

		Medical Officer	
		Ceftazidime	Moxalactam
Clinical Response*			
Urinary Tract Inf.	Complicated	13/13	9/11
	Uncomplicated	14/14	6/6
Bacterial Septicemia		5/7	7/7
Resp. Tract Inf.	Upper	-	0/1
	Lower	2/2	8/10
Fever Undeter. Origin		1/1	-
Intra-abdominal		2/2	
Gen. Urinary Infect.		1/1	
Total		39/40 (97.5%	32/37 (86.5%)
Bacteriological Response**			
Complicated UTI			
E. coli		1/1	3/4
Klebsiella species			1/1
P. mirabilis		1/1	
Providencia species			
P. aeruginosa			0/1
Uncomplicated UTI			
E. coli		6/6	
P. mirabilis		1/1	1/1
Klebsiella species		1/1	
Bacterial Septicemia			
E. coli		3/3	3/3
Klebsiella species		1/1	4/4
P. mirabilis			1/1
Enterobacter species		1/1	3/3
P. aeruginosa			1/1
Acinetobacter			1/1
S. aureus		0/1	
b hemo strep		1/1	
Achromobacter		1/1	
Serratia species		1/1	1/1
Total		8/9 (88.8%	14/14 (100%)
Intra-abdominal			
Peptostreptococcus		1/1	
Lower Resp. Tract Infect.			
E. coli		1/1	2/2
Enterobacter		1/1	
Pasteurella multocida			1/1

*Cured or improved/No. qualified
**No. of isolates eradicated/No. of isolates qualified

10. Neutropenic Studies

a) Study No. CAZ-N01 Phillip A. Pizzo, M.D., Head of the Infectious Disease Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland, conducted a randomized, controlled study to compare ceftazidime with a regimen of cephalothin, gentamicin, and carbenicillin in the treatment of febrile granulocytic patients. Cancer patients undergoing treatment in the pediatric, medical, or radiation branches of the clinical oncology program with the following criteria were selected:

1. Fever - Either three temperatures at least 38°C during a 24-hour period, or a single temperature elevation of 38.5°C or higher.

2. Granulocytopenia - Less than 500 polymorphonuclear leukocytes and band forms per mm^3. Patients who became febrile while counts of between 500-1000 PMNs/mm^3 were falling following chemotherapy could be selected.

Patients who were excluded were those with aplastic anemia, those without granulocytopenia, those with an allergy to cephalosporins, and those with impaired renal function.

After a complete diagnostic evaluation, patients were randomly assigned to two groups to receive either:

Ceftazidime: 90 mg/kg/day q 8 h IV for 10-14 days
(The upper limit was 6 g/day), or
Cephalothin - 170 mg/kg/day IV q 4 h (up to 12 g/day), plus
Gentamicin - (Upper limit 120 mg q 6 or q 8 h) Adjusted by blood levels.
Under 25 years of age - 6 mg/kg/day in divided doses q 6 h IV (Adjusted for renal function)
Over 25 years of age - 4.5 mg/kg/day in divided doses q 8 h IV, plus
Carbenicillin - 500 mg/kg/day in divided doses q 4 h IV. Not to exceed 36 g/day.

The treatment period was 10-14 days. All patients younger than 12 years old were to receive the standard triple regimen.

The pretreatment evaluations included history; physical examination; CBC with differential and platelet count; urinalysis; chest radiograph; serum chemistries; serum for storage (10 cc); cultures from nose, throat, urine, stools (or rectal swab) for fungi and ova and parasites; two blood cultures from separate sites; biopsy of obvious approachable lesions; and specimens for viral cultures. Lumbar punctures and lung biopsies were performed as needed.

Patients were classified as those with documented infections or fevers of undetermined origin.

There were 112 febrile episodes in 86 patients. Twenty-six patients were treated separately for recurrent febrile episodes. The admitting diagnosis for most patients was fever of undetermined origin. Eighty-one of 82 patients do not qualify for the microbiological evaluation because no organism was isolated.

Neutropenic Studies

	N01 Pizzo		N02 Ramphal		N03 Bodey		N08** Bodey				
							Part I		Part II		
	CAZ	CGC	CAZ	CGC	CAZ	C&T	CAZ	C&T	CAZ	C&T	C&V
Total	57	55	24	24	51	47					34
Age (yrs.)											
Under 2	-	-	-	-	-	-					
2-12	3	4	-	-	-	-					
13-18	9	11	-	-	1	1					4
18-25*	9	9	5	4	4	2					4
26-35	9	4	3	2	7	8					8
36-50	6	5	5	6	11	9					2
51-65	20	18	4	11	18	22					12
Over 65	1	4	7	1	10	5					4
Mean	37.4	37.8	48.4	47.2	50.8	49.4					43.3
Sex M	33	32	12	11	35	25					14
F	24	23	12	13	16	22					20
Mean Duration (Days)	8.2	9.0	13.9	14.1	7.4	7.9					7.5
Concurrent Disorders (%)											
Neoplasia	100%	100%	95.8%	91.7%	100%	97.8%					100%
Renal Dys-function	12.3%	5.5%	4.2%	8.3%	0	0					

*19-25 in Dr. Pizzo's study.
**Study No CAZ-N08 was incompletely analyzed.

The clinical response for 104 patients that were qualified for analysis is shown below is as reported by the applicant:

Infection	CAZ*	CGC*
Fever Undeter. Origin	32/64	39/41
Bacterial Septicemia	6/10	3/3
Skin & Skin Structure	2/3	3/3
Lower Respiratory Tract	0/1	2/3
Intra-Abdominal		0/1
Upper Resp. Tract		3/3
TOTAL	40/50 (80%)	50/54 (93%)

*No. Cured or Improved/No. Qualified

The applicant and medical officer report microbiological cures for qualified isolates as follows:

	Applicant		Medical Officer	
	CAZ	[illegible]	CAZ	[illegible]
S. epidermidis	0/1	2/2	-	1/1
S. viridans	-	1/1	-	-
Streptococci	-	1/1	-	-
E. coli	3/3	-	-	-
Klebsiella sp.	1/1	-	-	-
P. aeruginosa	1/1	-	-	-
Clostridium sp.	1/1	-	1/1	-
S. aureus	-	2/2	-	2/2
Salmonella sp.	-	1/1	-	1/1
TOTAL	6/7	7/7	1/1	4/4

The applicant concludes that the results of this trial show that there is no significant difference in clinical efficacy between groups. The assessment of drug safety is difficult in this patient population.

Reviewer's Comments:

1. The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Pizzo	#0178-029	E. coli	Cure	p 21-109
Pizzo	#0178-029	P. aeruginosa	Cure	p 21-109
Pizzo	#0178-080	E. coli	Cure	p 21-110
Pizzo	#0178-212	S. epidermidis	Failure	p 21-111
Pizzo	#0178-218	Klebsiella sp.	Cure	p 21-111

Cephalothin/Gentamicin/Carbenicillin

Pizzo	#0178-217	S. epidermidis	Cure	p 21-117
Pizzo	#0178-217	S. viridans	Cure	p 21-117
Pizzo	#0178-217	Streptococci	Cure	p 21-117

With these disqualifications, there remain only five cases that are qualified for the microbiological evaluation, one ceftazidime-treated case and four cases in the control group.

2. The 6 mg/kg/day gentamicin dose for patients under 25 years of age exceeds the dose which is recommended in gentamicin labeling. However, if the protocol was followed, the dosage adjustment according to gentamicin serum concentrations would make this high dose acceptable.

b) Study No. CAZ-NO-2 Reuben Ramphal, M.D., Assistant Professor, Department of Medicine, University of Florida, Gainesville, Florida, conducted a randomized, non-blinded, controlled study to compare ceftazidime with a regimen of cephalothin, gentamicin, and carbenicillin in the treatment of febrile granulocytic cancer patients at Shands Teaching Hospital or Gainesville Veterans Administration Hospital. This study was similar to study No. CAZ-NO1, above.

Reviewer's Comments: The protocol which has been filed was filed by mistake. It outlines a study with a control regimen of cefazolin, amikacin, and carbenicillin instead of the regimen which was used. In response to my request the correct protocol was filed in the amendment dated October 30, 1984.

Patients received either

Ceftazidime: 2.0 g IV q 8 h, or
Cephalothin: 170 mg/kg/day (up to 12 g/day) IV, plus
Gentamicin - 2 mg/kg IV q 8 h, plus
Carbenicillin - 500 mg/kg/day (up to 36 g/day) IV q 4 h.

Demographic information about this population is shown in the table above. As in the previous study, most cases are disqualified from the microbiological evaluation because no pathogen was isolated. Ceftazidime-resistant clostridia were the cause of superinfections in four cases, three of the four patients subsequently expired. The applicant's analysis of the clinical response and microbiological response are shown in the following tables.

Clinical Response

Infection	CAZ*	CGC*
Fever Undeterm. Origin	9/3	11/17
Bacterial Septicemia	1/7	2/4
Lower Respiratory Tract	1/1	2/3
Skin and Skin Structure	0/4	-
Total	11/25	15/24

*No. cured or improved/No. qualified

Microbiological Response

Pathogen	Applicant CAZ*	Applicant CGC*	Medical Officer CAZ	Medical Officer CGC
P. aeruginosa	1/1	1/1	1/1	1/1
E. coli	1/1	1/1	1/1	1/1
klebsiella species	1/1	-	1/1	-
S. aureus	-	1/1	-	1/1
S. viridans	-	1/1	-	-
Enterococci	-	1/1	-	-

*No. of isolates eradicated/ No. qualified

The applicant concludes that in this limited trial there was no clear difference between the clinical and microbiological outcomes for these groups. Since, there were four cases of clostridial superinfection due to organisms resistant to ceftazidime, the results suggest that ceftazidime should most likely be administered concomitantly with an agent that is active against Clostridium species.

Reviewer's Comments: The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Cephalothin/Gentamicin/Carbencillin

Ramphal	#0158-011	S. viridans	Cure	p 21-170
Ramphal	#0158-011	enterococci	Cure	p 21-170

c) Study No. CAZ-N03 Gerald P. Bodey, M.D., Chief, Section of Infectious Diseases, Department of Developmental Therapeutics, M.D. Anderson Hospital and Tumor Institute, Houston, Texas, conducted a randomized, controlled trial to compare ceftazidime alone with a regimen of ceftazidime plus tobramycin in the treatment of documented or presumed infections in non-neutropenic cancer patients. Hospitalized patients 14 years of age or older, with normal neutrophil counts and with proven or suspected infections, were assigned to groups to receive either

Ceftazidime: 2.0 gm IV q 8 h, or
Ceftazidime: 2.0 gm IV q 8 h plus
Tobramycin: 4.5 mg/kg/day. Dosage was to be adjusted.

Neutropenic patients were to receive ceftazidime in doses of 1 gm IV q 4 h.

Patients who responded to therapy were to be treated for sever days or for four days after becoming afebrile, whichever was longer. Patients showing evidence of progression of the infection after 60-72 hours were considered failures. Patients with an unchanged fever pattern after five days were considered failures.

Exclusions were similar to those given above and included patients with FUO

which was not likely to be due to bacterial infection. Pretreatment, during-treatment, and post-treatment evaluations were similar to those given above. The majority of patients selected for this study had lower respiratory tract infections or fever of undetermined origin. Demographic information is shown in the table above.

Clinical Response According To the Applicant
(Cured or Improved)

	CAZ	C&T
Pneumonia	6/13	13/16
Fever Undetermined Origin	16/18	8/11
Bacterial Septicemia	4/6	7/9
Urinary Tract Infection	2/2	2/2
Other	4/5	2/5
Total	32/44 (73%)	32/42 (74%)

Microbiological Response

	Applicant		Medical Officer	
	CAZ	C&T	CAZ	C&T
H. infuenzae	-	1/1	-	-
S. pneumoniae	-	2/2	-	1/1
P. mirabilis	1/1	1/1	-	1/1
P. aeruginosa	2/2	-	1/1	-
E. coli	-	1/1	-	1/1
Klebsiella sp	-	2/2	-	2/2
P. cepacia	1/1	-	-	-
S. aureus	1/1	1/1	1/1	1/1
S. epidermidis	1/1	-	1/1	-
Total	6/6	8/8	3/3	6/6

The applicant concludes that eradication rates between the two groups were identical with all evaluable pathogens being eradicated. The clinical responses were essentially the same. Results suggest that the addition of tobramycin to ceftazidime treatment does not provide an additional benefit over ceftazidime alone. Potential tobramycin adverse reactions are avoided.

Reviewer's Comments: The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Bodey	#0010-013	P. cepacia	Cure	p 21-230
Bodey	#0010-111	P. aeruginosa	Cure	p 21-230
Bodey	#0010-123	P. mirabilis	Cure	p 21-230

Ceftazidime/Tobramycin

Bodey	#0010-144	H. influenzae	Cure	p 21-239
Bodey	#0010-192	S. pneumoniae	Cure	p 21-240

d) Study No. CAZ-N08 Dr Bodey conducted a study like study No. CAZ-N04 in netropenic cancer patients. The first half of the study was conducted to evaluate ceftazidime alone and ceftazidime plus tobramycin. The second half of the study was conducted to evaluate ceftazidime plus vancomycin and ceftazidime plus tobramycin. In the first half of the study, patients were randomly assigned to treatment groups to receive either

Ceftazidime: 1.0 g IV q 4 h alone, or
Ceftazidime: 1.0 g IV q 4 h plus
Tobramycin: 60 mg/m^2 IV (1/2 hr. infusion) followed by 180 mg/m^2 (12 hr. infusion) q 12 h.

In the second part of the study, patients were randomly assigned t receive one of the following three regimens:

Ceftazidime: 1.0 g IV q 4 h, or
Ceftazidime: 1.0 g IV q 4 h plus
Tobramycin: 60 mg/m^2 IV (1/2 hr. infusion) followed by 180 mg/m^2 (12 hr. infusion) q 12 h, or
Ceftazidime: 1.0 g IV q 4 h plus
Vancomycin: 500 mg IV q 6 h.

Demographic information for two of the four groups is shown in the table above. Case reports are filed for 167 treatments for 150 patients. Eighteen isolates were evaluable for the microbiological evaluation.

Reviewer's Comments:

1. The applicant's analysis of this study is not acceptable because the ceftazidime cases and the ceftazidime/tobramycin cases from both parts of the study were lumped together and were not properly separated. The comparison of the ceftazidime-alone group with the regimen of ceftazidime plus tobramycin should have been analyzed separately as the first part of the study. Then, the three part comparison of ceftazidime alone, versus the regimen of ceftazidime plus tobramyin, versus the regimen of ceftazidime plus vancomycin should have been analyzed separately as the second part of the study. Since treatments were randomized and the second part followed the first part in time, they should not be pooled.

2. The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Bodey	#0010-534	P. aeruginosa (Septicemia)	Cure	p 21-313

Bodey	#0010-534	P. aeruginosa (Cellulitis)	Failure	p 21-313
Bodey	#0010-581	S. pneumoniae	Cure	p 21-314
Bodey	#0010-639	S. aureus	Cure	p 21-315

Ceftazidime/Tobramycin

Bodey	#0010-684	b. hemo. Strep	Cure	p 21-322

3. Since the applicant only found eighteen isolates to be evaluable, and the medical officer further disqualifies the above five isolates, the remaining 13 qualified isolates would have to be distributed between five treatment groups. Therefore, no efficacy conclusion could be drawn from this small number of cases.

11. Pediatric Studies

a) Study No. CAZ - S11 William J. Rodriquez, M.D., Children's Hospital, National Medical Center, Washington, D.C., conducted a randomized, non-blinded, controlled study of ceftazidime and a regimen of oxacillin plus chloramphenical in the treatment of acute skin and skin structure infections in pediatric and adolescent patients. Hospitalized patients were randomly assigned to two groups to receive

Ceftazidime: 30 mg/kg (up to 1 gm) IV q 8 h for 5-14 days, or
Oxacillin: 150 mg/kg/day IV in divided doses q 6 h, plus
Chloramphenical: 50-100 mg/kg/day IV in divided doses q 6 h.

Four cases were reported. All had cellulitis. Three received ceftazidime, two males and one female. Two were 11 months old and one was 2 years old. The mean treatment period was 7.7 days. All three were clinical cures. The applicant reports two isolates to be evaluable, S. pneumoniae and H. influenzae and both were eradicated by ceftazidime.

The 20 month old male treated in the control group for 15 days was clinically cured. He was disqualified from the microbiological evalaution.

Reviewer's Comments: The reviewer disqualifies the S. pneumoniae isolate (Case #0299 - 001) because susceptibility was not reported.

	Pediatric Studies							
	S11 Rodriquez		N01 Lange		N04 Nelson		N05 Gardner	
	CAZ	OC	CAZ	CGC	CAZ	TNT	CAZ	CGC
Total	3	1	9	11	13	17	2	2
Age								
Under 1 mo.	-	-	-	-	-	-	-	-
1-6 mo.	-	-	-	-	1	3	-	-
7-11 mo.	2	-	-	-	1	1	-	-
1-2 yrs.	1	1	2	2	1	6	-	-
3-6 yrs.	-	-	3	4	6	2	-	-
7-12 yrs.	-	-	3	3	3	5	1	1
13-18 yrs.	-	-	1	1	1	-	1	1
Over 18 yrs.	-	-	-	1	-	-	-	-
Mean (yrs.)	1.3	1.7	6.8	7.2	5.5	3.5	13.5	8.0
Sex M	2	2	5	3	6	6	1	1
F	1	-	4	8	7	11	1	1
Mean Duration (Days)	7.7	15	6.9	9.5	6.7	6.5	8.5	6.5
Concurrent Disorders (%)								
Neoplasia	-	-	100%	100%	61.5%	52.9%	100%	100%

b) Study No. CAZ-N01 Beverly J. Lange, M.D., Assistant Physician, Division of Oncology, The Children's Hospital of Philadelphia, PA, conducted a randomized controlled study to compare ceftazidime and a regimen of cephalothin, gentamicin, and carbenicillin in the treatment of febrile granulocytopenic pediatric patients. Her protocol is the same as Dr. Pizzo's protocol for Study No. CAZ-N01 except that in this study all pediatric patients were randomly assigned to treatment groups. Drug groups were

Ceftazidime: 30 mg/kg/ q 8 h (up to 6 g daily) IV, or
Cephalothin: 170 mg/kg/day (up to 12.0 g/day) IV divided q 4 h, plus
Gentamicin: IV divided q 6 h
Under 25 yrs old - 6 mg/kg/day
25 years old and over - 4.5 mg.kg.day, plus
Carbenicillin: 500 mg/kg/day (Up to 36.0 g) IV divided q 4 h.

Demographic information is given in the table above.

The applicant reports that none of the nine ceftazidime-treated patients were qualified for the microbiological analysis. Three of the eleven control cases were qualified and all three pathogens were eradicated. Pseudomonas maltophilia, Acinetobacter strain, and S. aureus.

A Clinical cure or improvement was reported for 6 of 7 (71%)

ceftazidime-treated cases and for 10 of 11 (82%) control-regimen cases. No conclusion can be drawn from this study.

Reviewer's Comment: The reviewer found the following two applicant-disqualified control drug isolates to be qualified:

Lange	#0273-009	E. coli	Cure	p 22-115
Lange	#0273-009	P. aeruginosa	Cure	p 22-115

c) Study No. CAZ-N04 John D. Nelson, M.D., Professor of Pediatrics, The University of Texas Southwestern Medical School, Dallas, Texas, conducted a randomized, controlled, efficacy and multiple-dose pharmacokinetic study of ceftazidime and a regimen of tobramycin plus ticarcillin in the treatment of gram-negative infections in pediatric patients with or without malignancies. Pediatric patients in Parkland Memorial Hospital or Children's Hospital in Dallas diagnosed as having gram-negative infections were assigned to receive

Ceftazidime: 225 mg/kg/day (Up to 6g daily) IV divided q 8 h, or
Tobramycin: 6 mg/kg/day (up to 300 mg/day) IV or IM divided q 6 h, plus
Ticarcillin: 300 mg/kg/day (up to 18 g/day) IV divided q 6 h.

Ceftazidime and tobramycin peak and trough serum concentrations were to be obtained on treatment days 2 or 3 and after 7 to 10 days of treatment. Ceftazidime levels were reported but were not summarized. Tobramycin dosage was adjusted.

Diagnoses were confirmed by culture and other appropriate studies and cultures were repeated at the completion of therapy. Neonates, patients with meningitis or cystic fibrosis, and patients who were hypersensitive to beta-lactam antibiotics were excluded.

The patient population was stratified into two groups, oncology patients and non-oncology patients. One 5-year old female with malignant lymphoma was enrolled three times for ceftazidime treatment (cases #2, 4, and 7). A 3-year old female with aplastic anemia was enrolled twice, once in the tobramycin/ticarcillin group (case #9) and once in the ceftazidime group (case #15). This latter treatment was a break in the randomization as were two other treatments, cases #11 and #36.

Only three isolates were evaluable. In the ceftazidime group, an E. coli strain causing septicemia and an S. aureus strain causing osteitis were eradicated. P. aeruginosa causing septicemia in the control group was eradicated. All three were clinical cures.

No conclusion can be drawn on the basis of this study.

d) Study No. CAZ-N05 Renee V. Gardner, M.D., Assistant Professor, Division of Hematology/Oncology, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida, conducted a randomized, controlled study to compare ceftazidime with a regimen of cephalothin plus gentamicin plus carbenicillin in the treatment of febrile granulocytic

pediatric patients. Hospitalized patients were randomly assigned to groups to receive either

Ceftazidime: 30 mg/kg IV four times a day (up to 6 g/day), or
Cephalothin: 100 mg/kg/day (up to 8 g/day) IV, plus
Gentamicin: 3.0 mg/kg IV q 6 h (Adjusted by serum levels), plus
Carbenicillin: 400 mg/kg/day (up to 30 g/day) IV.

Demographic information is shown in the table above. Four patients were treated, two in each group. Three had fever of undetermined origin and one had bacterial septicemia. Only one patient was qualified for the efficacy evaluation. This was a ceftazidime-treated case of Klebsiella septicemia and the organism was eradicated. Three of the four had a symptomatic cure. One improved.

No conclusion can be drawn from this study.

Uncontrolled Clinical Trials

1. Lower Respiratory Tract Infections and/or Septicemia

a) Study No. CAZ-R02 Ceftazidime was evaluated in the treatment of lower respiratory tract and/or systemic bacterial infections.

William J. Mogabgab, M.D., Tulane University School of Medicine, New Orleans, LA, treated 7 adult patients.

David Katz, M.D., Upsilanti, MI, treated 20 adult patients.

b) Study No. CAZ-R05 Ceftazidime was evaluated in the treatment of severe lower respiratory tract and/or systemic bacterial infections.

Michael C. Bach, M.D., Maine Medical Center, Portland, Maine, treated 14 adult patients.

Peter P. McKellar, M.D., Division of Infectious Diseases, Good Samaritan Hospital, Phoenix, AZ, treated 7 adult patients.

Gordon M. Trenholme, M.D., Associate Professor of Medicine and Pharmacology, Rush Presbyterian - St. Luke's Medical Center, Chicago, Il, treated 10 patients.

c) Study No. CAZ-R31 Francis Pierre Victor Maesen, M. D., Department of Respiratory Disease and Microbiology, DeWever Hospital, Heerlen, The Netherlands, treated 47 adult patients in the evaluation of ceftazidime in acute bacterial exacerbations of chronic respiratory tract infections due to Pseudomonas strains.

2. Skin and Skin Structure Infections and/or Septicemia

Study No. CAZ-S05 A multicenter study was conducted to evaluate ceftazidime in the treatment of serious infections of skin and skin structure and/or

systemic bacterial infections.

Michael C. Bach, M.D., Maine Medical Center, Portland, Maine, treated 16 patients.

Lawrence J. Eron, M.D., Fairfax, Virginia, treated 11 patients.

3. Urinary Tract Infections

Study No. CAZ-U06 Ceftazidime was evaluated in a multicenter study of the treatment of urinary tract infections

Matthew E. Levison, M.D., Medical College of Pennsylvania, Philadelphia, PA, treated 13 patients.

Paul B. Iannini, M.D., Danbury Hospital, Danbury, CT, treated 8 patients.

4. Bone and Joint Infections

a) Study No. CAZ-B01 Ceftazidime was evaluated in the treatment of bone and joint infections.

William J. Mogabgab, M.D. Tulane University School of Medicine, New Oeleans, LA, treated 22 adult patients.

Chien Liu, M.D., University of Kansas Medical Center, Kansas City, KA, treated 11 patients.

b) Study No. CAZ-B13 Ceftazidime was studied in the treatment of osteomyelitis and septic arthritis.

Jean Pierre Dutoy, Clinique Universitaire UCL, Mont-Godinne, Belgium, treated 15 adult patients.

5. Miscellaneous Infections

a) Study No. CAZ-A01 Ceftazidime was evaluated in the treatment of acute serious infections.

Harold C. Neu, M.D., Columbia University, New York, NY, treated 57 patients, ten of whom were under 12 years of age.

Chien Liu, M.D., University of Kansas Medical Center, Kansas City, KA, treated three patients.

b) Study No. CAZ-A02 Ceftazidime was evaluated in the treatment of acute infections.

Lowell S. Young, M.D., University of California at Los Angeles, Center for Health Sciences, treated 17 adult patients.

c) Study No. CAZ-A04 This was a clinical trial of ceftazidime as therapy for infections in nongranulocytopenic cancer patients.

Jai H. Joshi, M.D., University of Maryland Cancer Center, Un. of Maryland Hospital, treated nine patients.

d) Study No. CAZ-A06 A study of the effects of ceftazidime in patients with serious infections requiring a parenteral antibiotic was conducted in Canada.

Denis Phaneuf, M.D., Montreal, Canada, treated [illegible] patients.

Jean-Claude Pechere, M.D., Universite Laval, Quebec, Canada, treated 36 patients.

John Ruedy, M.D., St. Paul's Hospital, Vancouver, Canada, treated 10 patients.

Paul Chadwick, M.D., Microbiology Laboratories, Kingston General Hospital, Kingston, Ontario, treated four patients.

Michael A. Noble, M.D., Victoria General Hospital, Halifax, Nova Scotia, Canada, treated 26 patients.

e) Study No. CAZ-A60 Ceftazidime was evaluated in the tratment of serious bacterial infections.

Rolf A. Walstad, M.D., The Regional Hospital, Trondheim, Norway, treated 56 adult patients.

f) Study No. CAZ-A21 Ceftazidime was evaluated in the treatment of serious bacterial infections.

G. K. Daikos, M.D., Athens University School of Medicine, King Paul's Hospital, Athens, Greece, treated 20 patients.

g) Study No. CAZ-A23 This was a study of ceftazidime in the treatment of severe infections requiring a parenteral antibiotics.

Professor Jean Paul Butzler, Hospital Sainte Pierre. Brussels, Belgium, treated 27 patients.

h) Study No. CAZ-A29 Ceftazidime was studied in patients with serious infections requiring a parenteral antibiotics.

Professor A. M. Geddes, Department of Communicable and Tropical Diseases, East Birmingham Hospital, Birmingham, England, treated 77 adult patients.

6. Emergency Treatment

Study No. CAZ-A01 Ceftazidime was evaluated in the treatment of acute serious infections. The following 23 investigators treated the number of patients shown:

	Address	Patients treated
Gerald P. Bodey, M.D.	Houston, TX	3
Layne O. Gentry, M.D.	Houston, TX	7
Rodney M. Snow, M.D.	Birmingham, AL	1
Edward S. Johnson, M.D.	Newark, NJ	1
James J. Rahal, Jr., M.D.,	New York, NY	9
Thomas Nolen, M.D.	Columbiana, AL	5
Michael M. Grieco, M.D.	New York, NY	2
Michael C. Bach, M.D.	Portland, ME	-
Jeffrey L. Blumer, M.D.	Cleveland, OH	3
H. Preston Holley, Jr., M.D.	Charleston, SC	-
David N. Gilbert, M.D.	Portland, OR	-
Robert E. Winters, M.D.	Santa Monica, CA	-
Eskild A. Petersor, M.D.	Tucson, AZ	1
William H. Greene, M.D.	New Haven, CT	-
Corstiaan Brass, M.D.	Buffalo, NY	-
Jon T. Mader, M.D.	Galveston, TX	1
Joseph S. Solomkin, M.D.	Cincinnati, OH	1
Daniel J. Sexton, M.D.	Oklahoma City, OK	2
Ronald Blanton, M.D.	Cleveland, OH	1
John F. Modlin, M.D.	Boston, MA	1
Barbara J. Berger, M.D.	Brooklyn, NY	1
Ronald M. Buckley, Jr., M.D.	Philadelphia, PA	1
Kenneth H. Rand, M.D.	Gainesville, FL	1

7. Pediatric Studies

a) Study No. CAZ-R09 Ceftazidime was evaluated in the treatment of lower respiratory tract and/or systemic bacterial infections in pediatric patients.

Willis M. Gooch III, M.D., Primary Children's Medical Center, Salt Lake City, UT, treated 11 pediatric patients.

Thomas M. Nolen, M.D., Columbiana Clinic, Columbiana, AL, treated three patients.

Jeffrey L. Blumer, M.D., Pediatric Pharmacology Division, Rainbow Babies and Children's Hospital, Cleveland, OH, treated three pediatric patients.

b) Study No. CAZ-S06 Ceftazidime was evaluated in the treatment of skin and skin structure and or systemic bacterial infections in pediatric patients. The three investigators above conducted another study. Dr. Gooch treated 28 patients; Dr. Nolen treated four patients; and Dr. Blumer treated 20 patients.

c) Study No. CAZ-A01 Ceftazidime was evaluated in the treatment of acute serious infections.

John D. Nelson, Department of Pediatrics, The University of Texas Southwestern Medical School, Dallas, TX, treated seven pediatric patients.

Bacterial Septicemia Summary:

Concurrent bacterial septicemia was diagnosed in 151 patients participating in controlled trials. Two or more blood cultures positive for the same pathogen must have been obtained within 48 hours of the start of therapy. Of these, 77 isolates from ceftazidime-treated patients qualified for bacteriological evaluation as follows:

Bacterial Septicemia - Ceftazidime

	Total	R01	S01	R03	S03	R04	A03	S08	S09	M01	M03 M05	M02	M03
Total	77	22	1	2	5	11	9	2	2	18	2	2	1
E. coli	17	6		1	4	2	3	1					
Klebsiella sp.	3						1	1				1	
P. mirabilis	1	1											
S. pneumoniae	9	3		1						4	1		
Serratia sp.	5					4	1						
P. aeruginosa	4	1				2						1	
Pseudomonas sp.	1					1							
H. influenzae	10	2				1				6	1		
Enterobacter sp.	2	1					1						
N. meningitidis	6	1								5			
Acinetobacter sp.	2	1					1						
S. viridans	2	2											
B hem. strep.	2						1		1				
Moraxella sp.	1	1											
S. epidermidis	5	2	1		1								
S. aureus	3	2					1*						
Peptococcus sp.	1								1				
Salmonella sp.	2									2			
Hemophilus sp.	2					1				1			
Hemophilus sp.	2												

* The only failure was Case # 0237-001, a drug addict.

Reviewer Comment: In a re-review of the case reports to verify the applicant's numbers, the MO found six N. meningitidis septicemias instead of one and five S. epidermidis septicemias instead of three. These were organisms which the applicant had classified as "other" and which are now being tallied separately.

Forty-eight qualified isolates were analyzed from patients treated with the various control regimens as follows:

Bacterial Septicemia - Various Control Regimens

	Total	R03	S03	R04	S04	A03	S08	S09	M01 M05	N03	N03
Total	48	1	1	4	3	14	2	2	11	4	6
E. coli	10			3	1	3	1	1			1
Klebsiella sp.	9	1			1	4	1				2
P. mirabilis	3		1			1					1
S. pneumoniae	5								3	1	1
Serratia sp.	2				1	1					
P. aeruginosa	2			1		1					
H. influenzae	11								8	3	
Enterobacter sp.	3					3					
Acinetobacter	1					1					
S. aureus	1									1	
Bacteroides sp. (not frag.)	1							1			

There were 145 bacterial septicemia cases in uncontrolled clinical trials. Of these, 37 of 112 isolates were evaluable for bacteriological efficacy as follows:

	Cure	Failure	Total Evaluable	Not Evaluable	Total
E. coli	13	-	13	20	33
Klebsiella sp.	4		4	4	8
P. mirabilis	1		1	3	4
Enterobacter sp.	1		1	1	2
Citrobacter sp.	1		1		1
Serratia sp.	4		4	5	9
P. aeruginosa	3		3	13	16
S. epidermidis	3		3	2	5
Other	7		7	27	34
No growth				36	36
No sample				8	8
Total isolates	37		37	75	112

Adverse Reactions:

In these studies, drug safety was evaluated in 2648 patients who received ceftazidime and in 1051 patients who received the control regimens. Of these, 198 patients or 7.5% experienced one or more adverse events during the course of treatment. In 37 patients the adverse events were attributed to a cause other than ceftazidime. In the remaining 161, or 6.1% of patients, the cause of the event was unknown and was possibly or probably drug related. Adverse events were generally minor and were limited to (1) local reactions such as phlebitis or skin inflammation at the site of the injection, (2) hypersensitivity reactions such as rash and pruritis, (3) gastro-intestinal symptoms such as diarrhea or abdominal pain, and (4) rarely central nervous system involvement such as headache. The incidence of any one of these events was 2% or less.

Although ceftazidime has a wide spectrum of activity against aerobic micro-organisms, it is not highly active against anaerobes and it is not eliminated to any extent by biliary excretion. Consequently, ceftazidime is not expected to adversely affect gastro-intestinal flora to the point that antibiotic-associated colitis may develop. Of the 2648 patients, 36 experienced diarrhea. Diarrhea was the second most frequent adverse reaction.

Ceftazidime-Related Adverse Events Experienced by 161 Patients

Reaction	Number
Phlebitis/Local Inflammation	37
Diarrhea	36
Unspecified Rash/Urticarial Rash	34
Nausea	16
Headache	10
Pyrexia	10
Itching	8
Abdominal pain, non. spec.	6
Vomiting	5
Vaginitis, Urethritis	4
Monilial Overgrowth	4
Hyperglycemia	4
Colitis	3
Hypotension	3
Renal Failure	3
General Malaise	2
Dyspnea, shortness of breath	2
Allergic Exanthema	2
Itching Eyes	2
Feeling Hot	2
Tightness in Chest	2
Miscellaneous (Single reports)	27
Total	221

Miscellaneous single reports were hematuria, flushing, neutropenia, abnormal sensation of taste, feeling faint, bleeding, swelling of the hands, dizziness, bronchospasm, puffy/swelling eyes, hematemesis, glycosuria, pneumonia, pulmonary infiltrates, myeloid arrest, jaundice, cellulitis, thrush (oral), hallucinations, dry mouth, acute tubular necrosis, anorexia, swollen tongue, laryngeal edema, wheezing, and pain on injection.

The most frequently encountered abnormal laboratory values in ceftazidime-treated patients were eosinophilia and SGPT, SGOT, GGT, and LDH elevations. The clinical significance of these changes has not been determined.

There were seven patients with ceftazidime-associated prolonged prothrombin times. However, the prolongation in clotting time was only three seconds above the control in four of the seven patients and twelve seconds above the control in two patients. There were no bleeding events.

The most frequently abnormal laboratory findings in ceftazidime-treated patients (greater than 1% of the population) are listed below.

	% of Patients
Eosinophilia	7.4%
SGPT	6.7%
SGOT	6.1%
GGT	5.8%
LDH	5.5%
Alk. Phos.	4.3%
Direct Coombs'	4.3%
Thyroid Index	2.5%
Platelet Est.	2.2%
BUN	1.6%
Hematocrit	1.4%
Polys	1.3%
Bands	1.2%
Urinary rbc	1.2%

Amendments

Aug. 8, 1983 The applicant's address change notice is filed.

Dec. 7, 1983 The applicant requests reclassification of this Form 5 from 1 C to a 1 B category.

Feb. 7, 1984 Updated product stability information is filed.

Feb. 20, 1984 A letter scheduling a meeting on March 14, 1984 to discuss product stability information and expiration dating is filed.

April 4, 1984 Minutes of the March 14, 1984 meeting are filed.

May 29, 1984 The cephalosporin filling suite at Glaxo's Bernard Castle facility is expanded.

Aug. 13 and 24, 1984 Updated product stability information is filed.

June 8, 1984 The application is amended with eleven volumes to provide for the use of ceftazidime in the treatment of meningitis.

A study in rabbits of single intravenous doses or constant IV infusions of ceftazidime in doses of 50 mg/kg following intracisternal inoculations of either S. pneumoniae, H. influenzae, or E. coli revealed that therapeutic concentrations of ceftazidime of 4.1 to 14.0 mcg/ml were attained in CSF in the presence of inflamed meninges. The elimination of ceftazidime from the cerebrospinal fluid compartment is slower than the elimination from the intravascular space. Concentrations were effective in eradicating the micro-organisms.

A. Clinical Pharmacokinetic Studies for Meningitis: Three pharamcokinetic studies with a total of 24 patients were conducted. The first two were identical except for the dose and patient ages. The accompanying table shows the age and sex distribution.

1. Study No. CAZ-K09 Douglas L. Bechard, M.D., Erlanger Medical Center, Chattanooga, Tennessee, conducted a Phase I pharmacokinetic study to measure cerebrospinal fluid diffusion following single intravenous doses of ceftazidime and to measure diffusion after multiple doses in patients with bacterial meningitis. The diagnosis was confirmed by pretreatment lumbar puncture. Twelve patients were to receive ceftazidime in a dose of 75 mg/kg IV (maximum 2 grams) at different intervals before a repeat lumbar puncture twelve hours later. Actually, ten adults received a 2.0 gram dose and one three-month old infant received a dose of 300 mg in addition to their standard meningitis therapy. Serum samples were collected immediately after the infusion and again 1, 2, 4, and 6 hours later.

In the second part of the study CSF penetration was measured in one patient following multiple doses of 75 mg/kg (maximum 2 grams) q 8 h for 13 days. Serum and spinal fluid specimens were collected two hours after a dose.

	Meningitis								
	Pharmacokinetics			Efficacy					
	K09 Bechard CAZ	K13 Blumer CAZ	K14 Mayhall CAZ	M01 Rodriquez CAZ	M01 Rodriquez A/C	M03 Dajani CAZ	M03 Dajani A/C	M05 Blumer CAZ	M05 Blumer A/C
Total	11	10	3	47	27	4	3	1	2
Age									
Under 1 mo.		2		-	-	-	-	-	-
1-6 mo.		3		17	14	2	1	-	2
7-11 mo.		1		11	7	1	-	-	-
1-2 yrs.		2		9	3	-	1	1	-
3-6 yrs.		-		4	1	-	1	-	-
7-12 yrs.		-		4	2	1	-	-	-
13-18 yrs.		-		2	-	-	-	-	-
Under 18 yrs	1	-	-	-	-	-	-	-	-
18-25 yrs.	1	-	-	-	-	-	-	-	-
26-35 yrs.	-	-	-	-	-	-	-	-	-
36-50 yrs.	4	-	2	-	-	-	-	-	-
51-65 yrs.	5	-	-	-	-	-	-	-	-
Over 65 yrs.	-	-	-	-	-	-	-	-	-
Mean (yrs)	43.8	0.7	52.3	2.5	1.5	1.9	2.3	1.0	0.3
Sex M	4	5	1	28	19	4	2	0	1
F	7	5	2	19	8	0	1	1	1
Mean Duration (Days)	-	-	-	10.6	9.8	10.3	13.3	8.0	13.0

Results are reported in the following table:

Time	No. Cases	Mean Conc. (mcg/ml) Serum	Mean Conc. (mcg/ml) CSF	% CSF of Serum Conc.
Single Doses (Hours after dosing)				
2	3	57	3.6	6.3%
4	3	17	2.1	12 %
6	2	4.9	2.3	47 %
Multiple doses (Days)				
3	1	34.6	25.6	74 %
6	1	38.4	32.6	85 %
12	1	39.6	11.9	30 %

The applicant concludes that these data indicate that there are detectable concentrations in the cerebrospinal fluid after single intravenous doses. CSF concentrations were 3-15 times greater following repeat doses. This suggests that there may be slow elimation and some accumulation of ceftazidime.

There was no adverse reactions.

2. Study No. CAZ-K13 Jeffrey L. Blumer, M.D., Rainbow Babies and Children's Hospital, Cleveland, Ohio, conducted an identical study except that he studied pediatric patients who were all under 19 months of age and his dose was different. Patients received single doses of 47 to 58 mg/kg of ceftazidime intravenously in addition to the standard meningitis therapy. No patients were enrolled in the multiple dose portion of the study.

Results are reported in the following table:

Hours after Dosing	No. Cases	Mean Conc. (mcg/ml) Serum	Mean Conc. (mcg/ml) CSF	% CSF of Serum Conc.
2-3	3	25.3	3.5	13.8%
4	3	15.7	6.0	38.0%
6	3	17.1	6.0	34.9%
8	1	20	8.5	42.5%

There were no adverse reactions.

The applicant concludes that these data demonstrate that therapeutic cerebrospinal fluid concentrations of ceftazidime are attainable after the administration of a single dose to a patient with meningitis. Mean CSF concentrations rose to 6.0 mcg/ml at 4 hours and continued to rise over an eight-hour period.

3. Study No. CAZ-K14 C. Glenn Mayhall, M.D., Associate Professor of Medicine, Division of Infectious Diseases, School of Pharmacy and Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia, and coworkers, conducted a Phase I pharmacokinetic study to measure CSF concentrations in three adult neurosurgical patients. Hospitalized patients in the neurosurgery intensive care unit who had ventriculostomy tubes in place for the purpose of monitoring ventricular pressure were selected. None of these patients had meningitis and none were receiving other antimicrobial therapy. After baseline CSF samples had been obtained to determine the degree of meningeal inflammation, patients were given 2.0 g of ceftazidime IV over 30 minutes every 8 hours for three doses. Serum and CSF samples were collected at appropriate times.

Two subjects had intracerebral inflammation secondary to subarachnoid bleeding.

Results are shown below:

Ceftazidime Concentrations (mcg/ml)

Hours after Dosing	Subject #1 Serum	Subject #1 CSF	Subject #2* Serum	Subject #2* CSF	Subject #3 Serum	Subject #3 CSF
0	146	6.3	213	9	221	2.0
1	88	7.0	71	0.32	102	5.7
2	57	7.6	41	0.41	65	4.6
4	40	8.4	16	0.30	34	3.3
6	32	8.5	6.8	0.27	19	3.5
8	NA	NA	3.7	0.37	11	2.5

* No evidence of inflammation

There were no adverse reactions.

The applicant concludes that these data suggest that in the absence of inflamed meninges, significant CSF concentrations following intravenous doses are not achieved. Significant CSF concentrations are achieved in the presence of meningeal inflammation.

B Controlled Clinical Efficacy Studies of Meningitis:

Ceftazidime was compared with a regimen of ampicillin and chloramphenicol in three controlled trials.

1. Study No. CAZ-M01 William J. Rodriquez, M.D., Chief of Infectious Disease and Microbiological Research, Children's Hospital National Medical Center, Washington, D.C., conducted a randomized, controlled efficacy trial to compare ceftazidime and a regimen of ampicillin and chloramphenicol in the treatment of bacterial meningitis in infants and children primarily at Robert Reid Cabral Children's Hospital in Santo Domingo, Dominican Republic. Patients enrolled in the study were under the care of Jose Puiz, M.D., in San Domingo.

Hospitalized infants one month to 18 years of age who had clinical evidence of meningitis and in whom the causative organism was expected to be susceptible to ceftazidime, were selected. Symptoms were fever, irritability, seizures, nuchal rigidity and Kerning/Brudzinski signs.

Patients were randomly assigned to groups to receive either

Ceftazidime: 50 mg/kg (2.0 g maximum) IV q 8 h, or
Ampicillin: 300-400 mg/kg/day IV in 6 divided doses, plus
Chloramphenicol: 100 mg/kg/day IV in 4 divided doses.

Pretreatment blood and CSF specimens were obtained for culture. Follow-up specimens were obtained 24 to 48 hours after starting therapy, and periodically thereafter until negative or as indicated by the patients' condition.

Forty-seven patients were treated with ceftazidime and 27 were treated with the control. Nearly 80% of ceftazidime patients and nearly 90% of the control patients had concurrent disorders such as anemia, cachexia, and pneumonia, a function of the poor access to health care in the Dominican Republic. Meningitis was severe in 18 ceftazidime patients and in two control patients.

Cerebrospinal fluid ceftazidime levels for 10 of 47 patients ranged from 2.2 to 19.2 mcg/ml for samples obtained early in the course of therapy.

Results

	Applicant		Medical Officer	
	Ceftaz-idime	Ampicillin/ Chloram-phenicol	Ceftaz-idime	Ampicillin/ Chloram-phenicol
Clinical Outcome				
Cured	35 (94.6%)	20 (87%)		
Improved	1 (2.7%)	1 (4.3%)		
Failed	1 (2.7%)	2 (8.7%)		
No. Evaluable	37 (100%)	23 (100%)		
Bacteriological Outcome*				
Salmonella sp.	2/2	-	2/2	-
H. influenzae	16/16	10/10	13/13	10/10
Hemophilus sp.	1/1	-	1/1	-
N. meningitidis	8/8	2/2	7/7	2/2
S. pneumoniae	4/5	3/3	3/4	3/3
Total	31/32	15/15	26/27	15/15
%	96.9%	100%	96.2%	100%

*No. isolates eradicated/No. Qualified

Co-existent bacterial septicemia was diagnosed in 29 of these cases. Nineteen were evaluable and all causative pathogens were eradicated.

The only adverse reaction noted in the study was a case of diarrhea in a control patient. Four ceftazidime-treated patients experienced elevations in SGOT, one had a fall in platelet count, and one had eosinophilia. One control patient had an SGOT elevation. Thirteen ceftazidime patients and six control patients died while on therapy. None of the deaths were considered to be drug related but were considered to be due to the poor health of the population.

The applicant concludes that this study demonstrated that ceftazidime is as safe and effective in the treatment bacterial meningitis as standard therapy with a regimen of ampicillin and chloramphenicol. It is effective in meningitis due to H. influenzae, N. meningitidis, S. pneumoniae, and Salmonella species.

Reviewer's Comments: The medical officer disqualifies the following applicant-qualified isolates from the bacteriological evaluation because susceptibility was not reported:

Ceftazidime

Rodriquez	#0299-035	S. pneumoniae	Cure	p 1-160
Rodriquez	#0299-036	H. influenzae	Cure	p 1-161
Rodriquez	#0299-039	H. influenzae	Cure	p 1-161
Rodriquez	#0299-040	H. influenzae	Cure	p 1-161
Rodriquez	#0299-053	N. meningitidis	Cure	p 1-162

These five disqualifications change the eradication rate from 76.9% to [illegible]%.

2. Study No. CAZ-M03 Adnan S. Dajani, M.D., Director, Division of Infectious Diseases, Children's Hospital of Michigan, Detroit, Michigan, conducted a nonblinded, randomized, controlled, efficacy study to compare ceftazidime and a regimen of ampicillin and chloramphenical in the treatment of meningitis in infants and children over one month of age. Patients were randomly assigned to treatment groups to receive either

Ceftazidime: 50 mg/kg (2.0 g maximum) IV q 8 h, or
Ampicillin: 400 mg/kg/day IV (in 6 divided doses), plus
Chloramphenicol: 75 to 100 mg/kg/day IV (in 4 divided doses)

This study was similar to the one described above. Seven patients were enrolled and three were qualified for the microbiological evaluation. S. pneumoniae was eradicated in the one qualfied ceftazidime patient and H. influenzae was eradicated in two qualified control patients.

Adverse reactions in the ceftazidime group were rash, diarrhea, and nausea and vomiting. Diarrhea was reported for one control patient. Eosinophilia was reported for one ceftazidime patient.

The applicant concludes that these results suggest that ceftazidime may be effective in the treatment of S. pnuemoniae meningitis.

Reviewer's Comment: The mean age for the three patients in Dr. Dajani's control group (Ages 4yrs, 2yrs, and 5 months) should be 2.3 years instead of 0.3 years as given on page 1-213.

3. Study No. CAZ-M05 Jeffrey L. Blumer, M.D., Pediatric Pharmacology Division, Rainbow Babies and Children's Hospital, Cleveland, Ohio, conducted a nonblinded, randomized, controlled trial of ceftazidime and a regimen of ampicillin and chloramphenicol in the treatment of meningitis in infants and children. Patients were randomly assigned to receive either

Ceftazidime: 50 mg/kg (2.0 maximum) IV q 8 h, or
Ampicillin: 200 mg/kg/day IV in 4 divided doses, plus
Chloramphenicol: 100 mg/kg/day IV in 4 divided doses.

This study was similar to the two which were described above. Three patients were enrolled, one received ceftazidime and two received the control. All cases were cured and organisms were eradicated, ampicillin resistant H. influenzae in the ceftazidime case, and H. influenzae and S. pneumoniae in the control cases.

No adverse reactions were noted.

The applicant concludes that these limited results suggest that ceftazidime may be useful in the treatment of ampicillin resistant H. influenzae meningitis.

C. Uncontrolled Efficacy Studies of Meningitis

1. Study No. CAZ-M02 Gary Overturf, M.D., USC-LAC Medical Center, Pediatric Pavilion, Los Angeles, California, treated ten children 2 years of age and under for meningitis. The applicant reports that seven of seven qualified isolates were eradicated.

Reviewer's Comment: Five of the seven applicant-qualified isolates are disqualified by the reviewer because the susceptibility of the pathogen was not reported.

2. Study No. CAZ-A01 The following investigators received ceftazidime on a compassionate basis to treat individual cases of meningitis

Patricia Dubose, M.D., Northside Hospital, Atlanta, GA.
Barbara Berger, M.D., Brooklyn VA Hospital, Brooklyn, NY.
Roland Buckley, M.D., Pennsylvania Hospital, Philadelphia, PA.
Richard Jerauld, M.D., 300 North Prairie Avenue, Suite 615, Inglewood, CA.

The four patients ranged in age from 23 to 67 years. None of the cases were qualified for the bacteriological evaluation. Clinically, three patients were improved or cured. One patient failed to respond and expired after four days of therapy with ceftazidime and intrathecal amikacin. One patient experienced flushing.

There were 98 patients in these controlled and uncontrolled efficacy trials. The average daily dose was 150 mg/kg/day.

July 11 and 13, 1984 Artwork for ceftazidime labels and a copy of the quality control report for the 30-mcg discs are filed.

Sept. 5, 1984 In response to my request, the sponsor re-analyzed data in the original applications to exclude causative organisms for which susceptibility data were not available. In response to my request the applicant filed reports of statistical analyses of all studies in the

amendment. Statistically significant differences in bacteriological efficacy in favor of ceftazidime were found in the cefamandole comparative trial of lower respiratory tract infections (p = 0.05) and in the tobramycin/ticarcillin comparative trial for intra-abdominal infections (p = less than 0.001). No other significant differences were obtained in any of the other comparisons. In the clinical efficacy evaluations, the comparison of overall complicated urinary tract infections was significantly in favor of ceftazidime (p = less than 0.001). No significant difference was obtained in any of the other comparisons.

Sept. 21, 1984 Revised draft labeling is filed.

Oct. 30, 1984 In response to my request, the protocol for Dr. Reuben Ramphal's study N02 is filed.

Nov. 15, 1984 In response to our microbiologist's request, additional drug product samples have been sent to FOB-8.

Nov. 21, 1984 The application is amended to provide for the use of ceftazidime in the treatment of bacterial meningitis caused by Pseudomonas species. This report summarizes the European and U.S. experience with ceftazidime therapy in fourteen patients treated for meningitis due to Pseudomonas species, 13 compassionate cases and one controlled trial case.

The thirteen investigator are listed below.

William J. Rodriguez, M.D., Ph.D., Chief, Infectious Disease and Microbiology REsearch, Department of Pediatric Medicine, Children's Hospital National Medical Center, Washington, D.C.

Stephen J. Fedler, M.D., Department of Microbiology, The Royal Victoria Infirmary, Queen Victoria Road, Newcastle Upon Tyne , United Kingdom

J. L. Boaventura, M.D., Serv Infecto-Contagiosas, Santa Maria Hospital, Lisbon, Portugal

P. Francioli, M.D., Division de Maladies Infectieuses, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

George K. Daikos, M.D., First Department of Propedeutic Medicine, Athens University School of Medicine, Athens, Greece

Kjell Alestig, M.D., Associate Professor, Department of Infectious Diseases, University of Goteborg, Ostra Sjukhuset, Goteborg, Sweden

R. Donald Garrison, M.D., Assistant Professor, Department of Pediatrics, University of Florida College of Medicine, Jacksonville, FL

Emilio Bouza, M.D., Unidad de Enfermedades Infecciosas, Centro Especial "Ramon y Cajal", Carretera de Colmenar, Madrid, Spain

M. Gurgui Ferrer, M.D., Instituto Dexeus, Barcelona, Spain

Nicholas Rutter, M.D., M.B., M.R.C.P., Senior Lecturer in Child Health, Nottingham University and Nottingham City Hospital, Nottingham, United Kingdom

J. L. Barrio, Hospital Saint Paul, Barcelona, Spain

Daniel J Sexton, M.D., Oklahoma City Clinic, 701 Northeast Tenth Street, Oklahoma City, OK 73104

Michael Levine, M.D., Chief, Division of Infectious Disease, Sinai Hospital of Baltimore, Baltimore, MD

Three different protocols designed these studies. Patients received ceftazidime by intravenous infusion in doses of 50 mg/kg every 8 hours up to a maximum of 2 g of q 8 h. Pretreatment blood and CSF specimens and other laboratory studies were obtained for culture. Blood and CSF cultures were repeated during therapy and periodically until sterile. Each patient was monitored for safety and evaluated for efficacy. Patients ranged in age from 5 days to 72 years and included five infants and seven adults. The mean treatment period was 22 days.

Nine patients qualified for the clinical evaluation and all nine were cured. Eight patients qualified for the bacteriological evaluation and bacterial isolates from all eight were eradicated, five Pseudomonas aeruginosa isolates and three Pseudomonas species isolates.

One patient experienced diarrhea. The five-month old infant expired on the fifth day of treatment.

The applicant concludes that these data support the conclusion that ceftazidime is safe and effective for the treatment of meningitis due to Pseudomonas aeruginosa and Pseudomonas species.

Dec. 6, 1984 In response to the MO's request the adverse reaction summary table is amended and a summary table for adverse reactions with the control drugs is provided.

Dec. 11, 1984 The applicant filed a revised tissue/fluid level table for proposed drug labeling.

Drug Experience Amendments (Forms 1639): In keeping with current procedure, the sponsor has filed adverse reaction reports (Forms 1639) in the companion IND and has cross-filed these submission in the NDA. (These are not clinical trials reports.) Reports are listed below:

Feb. 2, 1984 Eight deaths, in critically ill patients, meningitis in four pediatric patients, cardiopulmonary arrest in two adults, cystic fibrosis in one patient, and legionellosis in one patient.

Feb. 15, 1984 Adverse reactions in three patients were confusion with progressive amnesia after bronchial instillation, reduced visual acuity, and

rash. All recovered. Effects may have been due to multiple concomitant drugs.

March 13, 1984 Thrombocytopenia and pericardial effusion in a child who was also on cimetidine, flucloxacillin, and hyosine-n-butylbromide.

March 26, 1984 Two deaths, cardiopulmonary arrest in a 2-month old infant after 4 days of treatment for meningitis, and in a 4-month old infant after one dose for meningitis.

April 23 and Aug. 13, 1984 Hearing loss was experienced on the eighteenth treatment day. The patient who experienced hearing loss received kanamycin and polymyxin B by irrigation just after a hearing defect was noticed.

April 24, 1983 Post-chemotherapy death due to pulmonary edema in an acute myologenous leukemia patient. Death was due to cystic fibrosis.

May 3, 1984 Patient recovered after a single grand mal seizure (had 5 concomitant drugs). Another patient who had elevated liver function test values (7 concomitant drugs) recovered.

May 3, 1984 Death due to renal failure in a bone marrow transplant patient who was also receiving cyclosporin, gentamicin, piperacillin, acyclovir, and furosemide. Also death due to renal failure of an acute lymphoblastic leukemia patient on cyclosporin. Another patient who had a temperature elevation recovered.

May 22, 1984 Unticarial rash in a 2-year old fibrocystic patient who recovered is reported.

May 23, 1984 Child with neutropenia recovered.

May 23, 1984 Six deaths were reported as follows: four children with meningitis who ranged in age from 2 months to 2 years, and two adult leukemia patients with fever of undetermined origin.

June 1, 1984 Renal failure followed treatment with cyclosporin A and ceftazidime. The patient is believed to have recovered after dialysis.

June 13, 1984 Interstitial nephritis due to piperacillin in one patient is reported.

June 21, 1984 Six deaths in cancer patients were not drug related.

June 21, 1984 Hypotension and reduced renal output experienced by one patients who died were not drug related.

July 24, 1984 Four reports are filed. Two deaths were candida septicemia in a patient on continuous peritoneal dialysis for chronic renal failure and septicemia related to acute renal failure. One patient recovered from an attack of angioedema. Seizures occurred after several days of therapy in the last report.

July 27, 1984 Two deaths were not drug related.

July 27, 1984 Death due to septicemia one month after treatment ended.

Aug. 2, 1984 Neutropenia necessitated withdrawal of the drug.

Aug. 7, 1984 After 18 days of treatment leukopenia developed and lasted 5 days in a patient with cystic fibrosis.

Aug. 17, 1984 Eight reports are filed. Deaths of two infants were due to meningitis (one patient received ampicillin instead of ceftazidime). Seizures attributed to azlocillin are reported. One patient with elevated lactate dehydrogenase died. One patient experienced eosinophilia and jaundice, one experienced GI bleeding. Two patients recovered from fever.

Aug. 17, 1984 Reports from the U.K. were filed as follows: death due to Clostridium difficile diarrhea in one patient, and death due to encephalopathy, twitching, and muscle disorder 24 hours after a road accident.

Aug. 29, 1984 Neutropenia resolved when the drug was stopped.

Sept. 4, 1984 Three cases of anuria in patients treated with oxacillin and ceftazidime are reported,

Sept. 12, 1984 Pseudomembranous colitis, hemorrhagic phenomena, death due to myocardial infection, dysfibrinogenemia, and death due to meningitis are reported.

Sept. 20, 1984 Pseudomembraneous colitis developed in a patient treated with a number of antibiotics. Necrotizing enterocolitis developed in a newborn 24 hours after ceftazidime was started. Upper GI bleeding occurred in a 5-day old male treated with vitamin K. The baby recovered. Weakness and paralysis developed in a child's arm 1-2 weeks after the end of treatment.

Sept. 24, 1984 Death in a fibrocystic patient was due to pneumonia.

Sept. 28, 1984 The following reports are filed: death due to metastatic CA of the heart, two deaths secondary to cystic fibrosis, death due to acute lymphatic leukemia, and death due to pulmonary edema.

Oct. 1, 1984 Necrotizing enterocolitis in a 30-day old infants who recovered was reported

Oct. 1, 1984 A 13-year old patient with a cerebellar abscess experienced tonic-clonic seizure movements of the arm for 2 days. She received.

Oct. 16, 1984 Pseudomembranous colitis was treated sucessfully with vancomycin. A patient with diarrhea for one day and an elevated Coomb's test recovered. Other reports were death due to leukemia, deafness due to amikacin, death five days after treatment due to hemorrhage and ruptured pulmonary artery, death due to Pneumocystis pneumonia which was not drug related, and death due to cardiovascular failure in an 84-year old immunosuppressed patient.

Oct. 23, 1984 Bilateral periorbital edema was reported without other information.

Oct. 23, 1984 Death 6 hours after admission was due to cardiopulmonary arrest.

Nov. 5, 1984 Death in a leukemia patient from gastro-intestinal bleeding and a death due to cardiac arrest are reported.

Nov. 5, 1984 Dysuria with macronematuria 24 hours after starting ceftazidime and vancomycin are reported from Switzerland.

Nov. 7, 1984 Death was due to histiocytosis.

Nov. 28, 1984 Death of a leukemia patient was due to hematuria. The patient received seven concomitant drugs.

Labeling Review: The reader is referred to the separate MOR of Labeling and Memoranda of Telephone Conversations December 1984.

Overall Medical Officer's Evaluations and Conclusions:

Ceftazidime appears to be an outstanding third-generation cephalosporin. Most of the data which have been filed by the applicant are supportive of labeling claims which have been proposed.

Those studies which represent substantial evidence for proposed labeling claims and which are felt to be adequate and well-controlled are listed below together with the applicant's and the medical officer's calculated eradication rates. (The table gives the number of organisms eradicated/ number of organisms qualified.)

Adequate and Well-Controlled Clinical Trials

Study # Claim	Ceftazidime Applicant	Ceftazidime Med. Off.	Control Group Control Drug	Control Group Applicant	Control Group Med. Off.
R03-LRI*	71/78 (91%)	71/78 (91%)	Cefamandole	42/46 (91.3%)	46/57 (78.9%)
R04 & -LRI* R07	53/62 (85.5%)	53/62 (85.5%)	Tobramycin & Ticarcillin	56/73 (76.7%)	55/71 (78.9%)
R10-Pneu-monia**	11/14 (78.6%)	11/14 (78.6%)	Tobramycin & Cefazolin	10/13 (76.9%)	10/13 (76.9%)
S03-SSTI*	80/89 (89.9%)	79/88 (89.8%)	Cefamandole	49/59 (83.1%)	52/62 (83.9%)
S04-SSTI*	30/33 (90.9%)	30/33 (90.9%)	Tobramycin & Ticarcillin	27/32 (84.4%)	27/32 (84.4%)
S07-SSTI	20/20 (100%)	20/20 (100%)	Moxalactam	19/20 (95.0%)	19/20 (95.0%)
S09-GYN*	55/58 (94.8%)	53/56 (96.2%)	Tobramycin & Clindamycin	57/60 (95%)	22/24 (91.7%)
S08*+M50 +S10 Int-Abdom.	83/84 (98.8%)	83/84 (98.8%)	Tobramycin & Clindamycin	74/100 (74.3%)	74/100 (74.3%)
U05-UTI	58/68 (85.3%)	58/68 (85.3%)	Tobramycin	55/60 (91.7%)	55/60 (91.7%)
B03-B&J	12/13 (92.3%)	12/13 (92.3%)	Tobramycin & Ticarcillin	7/7 (100%)	7/7 (100%)
M01-Men-ingitis	31/32 (96.9%)	26/27 (96.2%)	Ampicillin & Chloramphenicol	15/15 (100%)	15/15 (100%)

*These controlled trials included bacterial septicemia cases.
**Study No. P-10 had a third treatment group, a tobramycin/ticarcillin regimen in which two isolates were eradicated.

Other controlled studies which support these claims are listed below:

Study # Claim	Ceftazidime Applicant	Ceftazidime Med. Off.	Control Group Control Drug	Control Group Applicant	Control Group Med. Off.
RC3-LRI	3/3	3/3	Moxalactam	4/5	4/5
U07-UTI	7/8	7/8	Moxalactam	1/3	1/3
U08-UTI	5/7	5/7	Tobramycin	4/8	4/8
N01-Neutropenia	6/7	1/1	Cephalothin & Gentamicin & Carbenicillin	7/7	4/4
N02-Neu	3/3	3/3	Cephalothin & Gentamicin & Carbenicillin	5/5	3/3
S11-Pediatric	2/2	1/1		0/0	
N04-Pediatric	2/2	2/2	Tobramycin & Ticarcillin	1/1	1/1
N05-Pediatric	1/1	1/1		0/0	
M03-Meningitis	1/1	1/1	Ampicillin & Chloramphenicol	2/2	2/2
M05-Meningitis	1/1	1/1	Ampicillin & Chloramphenicol	2/2	2/2

Bacteriological results and eradication rates from uncontrolled trial data are summarized in the following table. These data strengthen the evidence from controlled trials for some of the micro-organisms which are to be included in the labeling. Cells in the table show the number of organisms eradicated over the number of organisms qualified.

Uncontrolled Trial Results

Organism	LRT	SSTI	UTI Complic.	UTI Uncom.	Septicemia	Bone & Joint	Intra-Abdominal	Endocarditis
E. coli	6/6	4/4	[illegible]	[illegible]	[illegible]	[illegible]	3/3	
Klebsiella sp.	15/15	6/7	[illegible]	2/2	4/4	[illegible]	2/2	
P. mirabilis	7/8	4/4	6/6	2/2	1/1	[illegible]		
Enterobacter	3/5	6/6	1/3		1/1	[illegible]		
Citrobacter	1/1	1/1					1/1	
H. influenzae	25/25							2/2
S. pneumoniae	13/13							
P. aeruginosa	32/42	26/30	19/24	4/4	3/3	31/35	2/2	
S. aureus	5/6	9/10				15/16		
Acinetobacter	2/2					1/1		
Pseudomonas sp.	2/2					1/1		
S. pyogenes		7/7						
B. hem. strep.		2/2						
Serratia sp.	6/6	5/5	2/3		4/4	2/3	1/1	
Proteus (Ind.+)	0/1	1/1	2/2			5/5	1/1	
Neisseria sp.	9/9							
S. epidermidis		1/1			3/3			
Salmonella sp.							2/2	
Other						5/6		
Total	127/143	74/81	63/72	25/25	37/37	74/82	14/15	2/2
%	(90%)	(91.4%)	(87.5%)	(100%)	(100%)	(90.2%)	(93.3%)	(-)

Clinical data and in vitro microbiological data in this application considered together are adequate to include the following claims and micro-organisms in the Indications and Usage section of the labeling.

1. Lower Respiratory Tract Infections, including pneumonia due to

Pseudomonas aeruginosa	E. coli
H. influenzae	Serratia species
Klebsiella species	Citrobacter species
Enterobacter species	S. pneumoniae
P. mirabilis	S. aureus (methicillin-susceptible strains)

2. Skin and Skin Structure Infections due to

P. aeruginosa	Citrobacter species
Klebsiella species	Serratia species
E. coli	S. aureus (methicillin-susceptible strains)
Enterobacter species	S. pyogenes (Group A beta hemolytic streptococci)
Proteus species	
P. mirabilis	

3. Urinary Tract Infections due to

Pseudomonas aeruginosa	Klebsiella species
Other Pseudomonas species	Serratia species
Enterobacter species	E. coli
Proteus species	P. mirabilis

4. Bacterial Septicemia due to

Pseudomonas aeruginosa	Enterobacter species
Klebsiella species	Serratia species
H. influenzae	S. pneumoniae
E. coli	S. aureus (methicillin-susceptible strains)
P. mirabilis	S. epidermidis (methicillin-susceptible strains)

5. Bone and Joint Infections due to

Pseudomonas aeruginosa	Serratia species
Klebsiella species	Enterobacter species
Proteus species	S. aureus (methicillin-susceptible strains)

6. Gynecological Infections including endometritis, pelvic cellulitis, and other infections of the female genital tract due to

E. coli	Klebsiella species
beta hemolytic streptococci	S. aureus (methicillin-susceptible strains)

Recommendation: It is recommended that Glaxo's application for ceftazidime be made approvable pending receipt of satisfactory labeling.

Theresa Greene Reed

Theresa Greene Reed, M.D., M.P.H.
Medical Officer, HFN-815

cc
Orig Form 50-57
HFN-815
HFN-815/Reed
HFN-815/Rhinehart
HFN-815/Norton
HFN-340/Kelsey
HFN-235
1238b and 2527b

and polymicrobial infections caused by aerobic and anaerobic organisms, including Peptococcus species, Peptostreptococcus species and Bacteroides species (Many strains of B. fragilis are resistant.)

7. Intra-abdominal Infections including peritonitis due to

Pseudomonas aeruginosa	Enterobacter species
E. coli	S. aureus (methicillin-susceptible strains)
Klebsiella species	

and polymicrobial infections caused by aerobic and anaerobic organisms, including Peptococcus species, Peptostreptococcus species and Bacteroides species (Many strains of B. fragilis are resistant.)

8. Central Nervous System Infections including meningitis due to

Pseudomonas aeruginosa	N. meningitidis
H. influenzae	S. pneumoniae

The following claims are not supported and are deleted from proposed labeling:

1. Lower Respiratory Tract Infections - Delete Acinetobacter species and other Pseudomonas species.

2. Skin and Skin Structure Infections - Delete other Pseudomonas species, Acinetobacter species, S. epidermidis, and polymicrobial infections caused by aerobic and anaerobic organisms including Peptococcus species, Peptostreptococcus species, and Bacteroides species.

3. Urinary Tract Infections - Delete Providencia species.

4. Bacterial Septicemia - Delete other Pseudomonas species and Salmonella species.

5. Bone and Joint Infections - Delete other Pseudomonas species and S. epidermidis.

6. Intra-abdominal Infections - Delete Clostridium species.

7. Central Nervous System Infections - Delete Salmonella species.

Deleted micro-organisms which are not mentioned elsewhere in the section should appear in the Microbiology section with an indication of microbiological activity but with a statement that the clinical significance is unknown.

PHARM

REV

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-578 (Original Submission dated 5/20/93)

Date Submission Received: 5/0/93

Date Review Completed: 9/1/93

Applicant: Glaxo, Inc., Research Triangle Park, NC

Drug: Fortaz™ (ceftazidime for injection); IV, IM

Category: Cephalosporin antibiotic

Related Submissions: IND 13,257

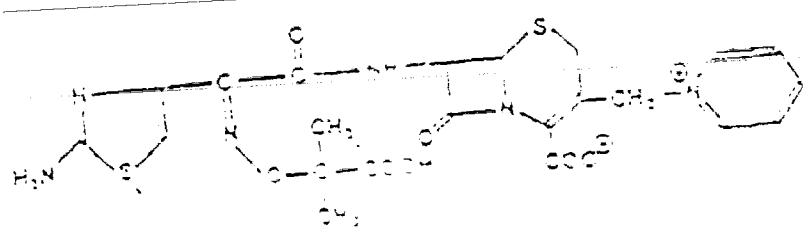
Chemistry: Fortaz™ contains ceftazidime pentahydrate, formulated as a sterile dry powder blend with anhydrous sodium carbonate. Supplied in vials (1.0 & 1.2g), infusion pack (1.2g) & 6g pharmacy bulk pack.

Chemical Formula

(6R,7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yloxyimino)acetamido]-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylate, pentahydrate

or the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]].

Structure



Proposed Clinical Use: Ceftazidime sodium (CTZ) is indicated in the treatment of bacterial infections caused by susceptible strains of microorganisms designated in the following [illegible].

Dosage

Adults: The usual adult dosage is to be administered IV or IM every 8 hrs. In severe infections or life-threatening situations, the dosage may be increased to 12 gm/day (100mg/kg/day in adults). In patients with impaired renal function (<50ml/min) the recommended dosage is reduced as follows:

Creatinine Clearance (ml/min/1.73m²)	Recommended Unit Dose of FORTAZ g	Frequency of Dosing Hourly
50-31	1.0	12
30-16	1.0	24
15-6	0.5	24
<5	0.5	48

Neonates, Infants and Children

The following dosage schedule is recommended:

Neonates (0-4 weeks of age)	30 mg/kg IV q 12h
Infants and Children (1 month - 12 years)	30-50 mg/kg IV q 8h to a maximum daily dose of 6 grams

The higher dose should be reserved for infections in immuno-compromised or fibrocystic children.

[illegible]

Previous Pharmacology Reviews on [illegible]

Submission	Date	Review Date	Reviewer
[illegible]	[illegible]	[illegible]	[illegible]

Review of Preclinical Studies Not Previously Reviewed in IND 10,257

Abbreviations: SS = statistically significant
NSS = not SS
DR = drug-related effect(s)
CFT = ceftazidime
CEF = cephaloridine
CEZ = cefazolin
I = increase
D = decrease
DR = drug-related
RA = radioactivity
CEF = cefuroxime
GTM = gentamicin

Pharmacology Studies: See review by Dr. G. James.

Pharmacokinetics

1. Miscellaneous: A comparison of 2 assay methods (microbiologcal vs. HPLC) and 2 batches of CFT (75% pure vs. 98% pure) was carried out on the plasma levels of CFT obtained by dosing dogs IM with the drug. The HPLC method was considered a suitable alternative to the microbiological method used for routine analysis. There was a SS difference between the 2 batches, in that the area under the curve was lower for the 75% pure drug as compared to the 98% pure drug.

2. Rat - SC: Rats were dosed SC with 20mg/kg of ^{14}C CFT and blood samples were obtained at 15-100' post-dosing. Plasma levels of CFT & RA were assayed by liquid scintillation & HPLC, respectively. The pharmacokinetic results of both methods indicated that there was no metabolism of CFT in the rat during the time period of the experiment. The elimination half-lives were in good agreement by both methods, i.e., 28' for radiolabel & 26' for parent drug.

3. Lactating Rat - SC: Lactating F rats (7 days post-parturition) were dosed SC with CFT at levels of 0, 0.1, 0.5 & 2.5g/kg. The CFT ratios (plasma:milk conc'ns) obtained at all doses ranged between 10:1 & 84:1 (mean 36:1). At 2.5g/kg there was a reduction in wt gain of pups during the first 21 days post-partum. However, this was attributed to maternal toxicity.

4. Rabbit - IV: Plasma levels of CFT were measured (5'-240') in rabbits dosed IV with 20mg/kg. Distribution was rapid and $t_{1/2}$'s were between 34 & 47'. The areas under the plasma level time curves (AUCs) were 6560-10170ug/ml and clearance values were 4.9-9.9ml/min; volumes of distribution were 130-150ml/kg.

5. Pregnant Rabbit - IV: Pregnant rabbits (controls, nonpregnant F) were treated IV with 20mg/kg of CFT on days 4, 8, 15, 22 & 29 of pregnancy (day 1 being the day of mating). Blood samples were taken at predosing and up to 3 hrs after dosing. On day 30, the pregnant ones received one more dose of 20mg/kg CFT and were killed 30' later. Pregnancy was not found to influence the t1/2, clearance & AUCs; however, the volume of distribution was SS higher on day 29 in the pregnant gp. Placental transfer of CFT into the rabbit fetus 30' after dosing was found to occur. The average ratio of dam:fetal plasma conc'n was ca. 20:1 (range [illegible]). The avg. ratio of dam plasma:fetal amniotic fluid level of [illegible] with a range of between 3:1 & [illegible].

6. Dog - IV: Plasma levels of CFT were measured in dogs at intervals up to 8 hrs after IV dose of 20, 40 & 80 mg/kg. The elimination t1/2 was between 50 & 80' at all dose levels. Peak plasma levels and AUCs showed a dose response relationship; however, total body clearance (ca. 4ml/min/kg) and volume of distribution were dose-independent.

7. Dog - IV: Dogs were dosed IV with 20mg/kg of ^{14}C CFT and blood was collected between 30' & 4 hrs post-dosing. The plasma conc'n time curves revealed that CFT, whether as parent drug (determined by HPLC) or radiolabel, was cleared from the plasma with a t1/2 of 45-50'. There was no evidence of significant metabolic transformation of CFT in the dog.

8. Rat - SC: M rats were dosed SC with ^{14}C CFT (20mg/kg) and exanguinated under anesthesia at 20, 40 & 80' after dosing; various organs were then removed. Plasma samples were assayed for their CFT content by HPLC. Accumulation of RA only appeared to occur in the kidney which contained ca. 2-3x as much RA as the plasma. There was no RA bound to the red cells over the time period studied. Plasma levels of CFT were in good agreement with ^{14}C levels, indicating that the majority of circulating RA was parent compound and there was little, if any, metabolism.

9. Rat - SC: M rats were treated with ^{14}C CFT (99% pure; 20mg/kg & 8 [illegible] mg/). RA & CFT levels were determined in plasma, liver & kidney between 4 & 96 hrs post-dosing. Liver & kidney levels were equiv. to roughly 0.5ug/g of CFT at 24 hrs & 0.2ug/g at 96 hrs. These results indicated an elimination half-life of ca. 3 days. By 96 hrs RA levels were similar to background levels. The overall results provided no strong evidence for metabolism of CFT. Moreover, these results refuted those of an earlier study in rats (GDH/82/006; Vol. 54, p.152) where much higher levels in the liver occurred (8x higher) and to a lesser extent in the kidney. These findings were attributed to using a low purity ^{14}C CFT (i.e., 99% pure).

10. Rat - SC (Repeated Dose): Three grps of rats were treated SC with ^{14}C CFT at 20mg/kg/day as follows:

(a) 10 doses of CFT over 10 days
(b) 9 doses of saline (9 days) & 1 dose of CFT on the 10th day
(c) 1 dose of CFT

[illegible] animals were killed 24 hrs later and blood, liver & kidneys were [illegible].

The 10 daily doses of ^{14}C CFT resulted in CFT equiv. conc'ns of ca. .5ug/g in liver & 2ug/g in kidney, which were about 2-3x higher than the levels after a single dose. Since plasma levels were higher in the grp [illegible], the [illegible] plasma RA level expected little [illegible] the 9 saline-dose grp and the 10-dose grp of animals.

11. Dog - IV (Pharmacoscintigraphy): Pets were dosed IV with [illegible] CFT at [illegible] were killed between 0 & 45' and 1 & 24 hrs after [illegible]; whole body autoradiography was performed.

^{14}C CFT was widely distributed in the various tissues and was considered similar to that seen after SC admin. (report COTA25 - see review by Dr. C. James; NDA 10.887). Fecal excretion occurred after 5' and still existed 24 hrs post-dosing. RA was secreted by the gastric mucosa into the lumen of the stomach and there was evidence of fecal excretion of RA. There was no evidence of CFT precipitating in the pulmonary circulation to form microemboli.

12. Rat - SC - Repeated Dose - Autoradiography: Rats (6/sex) were dosed SC with unlabeled CFT for 13 days at 2500mg/kg. On the 16th day, a similar injection + 1.79mg (12.85 UCi) of ^{14}C CFT/ml of dose sol'n was administered. Rats were killed between 5 & 24' post-dose and blood taken. On the 14th day, 2/sex rats were similarly treated with a single dose of labeled CFT and were killed at 15 or 60'. Whole body autoradiography was performed. The urinary tract (kidney, bladder, urine) appeared to be the more strongly labeled among the other systems. RA was widely distributed among the other organ systems in various degrees of low to moderate.

Under all the conditions studied, absorption from the injection site was rapidly established and RA were detected in the blood at 5'. In those rats given repeated high doses, RA persisted in the blood for at least 4 hrs, whereas those given a single dose had no detectable levels after 1 hr. RA was being excreted in urine in all cases by 5 min.

High respective doses of CFT did not increase the distribution of RA to the liver and did not promote biliary secretion. The secretion of RA by gastric mucosa was still obvious at 4 hrs in contrast to the absence of such secretion after 1 hr in those rats receiving only single doses.

These experiments demonstrated that while the distribution and excretion patterns after high doses were similar to those after single doses, RA persisted in the body for a longer period.

13. Pregnant Rat - IV - Autoradiography: Pregnant rats were treated on their 16th day of gestation with ^{14}C CFT at a dose of 16.8mg/kg. Rats were killed at 5-30' & 1-4 hrs post-dosing and blood was obtained. Whole body autoradiography was carried out. Plasma conc'ns of CFT peaked at 15' after dosing (30.5ug/ml) but none were detected in plasma 4 hrs after dosing. Small amounts of RA passed to the fetus and fetal conc'ns increased with time to peak at 2 hrs (whole individual fetuses were consumed for total RA counted). RA in fetuses was concentrated in the kidney & bladder with a low even distribution throughout the remaining fetal tissues, except the CNS, where no RA was detected.

14. Rat - SC - Urine: Two grps of rats were dosed SC with 20mg/kg CFT and [illegible] collected at 24 hrs with flasks containing distilled water or 1% acetic acid (acidic conditions). Another grp of rats was dosed SC with 20mg/kg of CFT and urine was collected "fresh" and then a further sample was allowed to stand at room temp., collection being then a 24-hr period.

77% recovery of CFT under normal collection conditions was increased to 90% when the urine was collected into the citric acid soln. This demonstrated that chemical degradation occurred after the urine was voided and could lead to an under-estimation of urinary excretion of CFT in the rat.

Scintillation counting of fractions of HPLC column eluant from the assay of fresh urine from rats dosed SC with ^{14}C CFT showed that the drug was excreted unchanged during the first 3.5 hrs after dosing. This period was equal to ca. 6 elimination half-lives of CFT in the rat. There was no evidence of elimination of metabolites of CFT in the urine of the rat.

15. Rat - SC - Bile: Biliary excretion of RA & parent drug was determined in 4 rats dosed SC with 100mg/kg of ^{14}C CFT. Maximum biliary excretion occurred 2 hrs post-dosing at a flow of 0.7ml/hr and the percentage of dose recovered in bile was less than 1% in the first 4-5 hrs. The majority of RA in the bile was attributable to CFT; however, there was clear evidence of metabolites in 1/4 rats in the 2-4 hr sample which accounted for about 0.1% of the administered dose.

16. Rat Enzyme Induction (Low Dose): SC admin. of CFT to rats 3x/day for 7 days (20mg/kg) did not have an inducing effect on hepatic microsomal mixed function oxidase enzymes, whereas these enzymes were induced by a combination treatment of phenobarbitone & B-naphthoflavone.

17. & 18: Rat Enzyme Induction (High Dose): Female rats received 500mg/kg/day SC of CFT or cefotaxime; controls were treated with distilled water (negative control) or a combination of phenobarbitone/B-naphthoflavone (positive control for enzyme induction; PB/BNF). CFT significantly increased some of the hepatic microsomal parameters in this study, i.e., I in O-demethylase activity, aniline hydroxylase activity (lower at 48hrs. & rel.); however, there were no significant I's due to cefotaxime. Nevertheless, this effect by CFT was very small compared to the positive control. Cholesterol levels were increased by all 3 treatments, i.e., except in the negative controls. Alkaline phosphatase was D in the positive control but I by cefotaxime, and aspartate transaminase was I by both of these treatments. Alanine transaminase was not I by any of the treatments. Rat liver glycogen levels were D by all 3 treatments, viz: PB/BNF to 37% of control levels, CFT & cefotaxime to 55 & 55%, respectively, of control levels.

19 & 20. In vitro, the half-life of CFT in rat & human plasma was determined at 37°C. The stability in rat & human plasma was similar at 4°C & room temp., but at 37°C, was more stable in human than rat plasma, the half-lives being 14 & 6 hrs, respectively. The stability of CFT was also investigated in rat & human urine at the same temp. as used for plasma. The greatest loss occurred in human urine at 37°C, in which 50% of [illegible] after 21 hrs. The implication of these findings [illegible] studies was that the instability [illegible] an underestimation of total excretion.

At high concns (1-2mg/ml) CFT produced positive interference (higher values) in the assay of standard Auto Analyzer method of creatinine, but only to a minor extent (ca. 5%).

2). [illegible]: Plasma levels in dogs receiving daily IV doses of CFT [illegible] in a 10-day toxicity study were monitored on the 9th day. The elimination half-life of the drug was approx 45' and plasma levels were dose-related. No metabolites were detected under the conditions employed.

Acute Toxicity Studies

Table 1

LD50 of CFT

	Species	Age	Route	LD50 (g/kg) Males	Females
(1)	Mouse	3 days	IP	4.6	6.1
		14 days	IP	4.9	4.8
		21 days	IP	9.0	8.4
(2)	Rat	3 days	IP	5.7	5.7
		14 days	IP	5.9	5.8
		21 days	IP	7.5	ca. 7.4
(2)	Rat	3 days	SC	ca. 6.3	ca. 6.3
		14 days	SC	6.6	7.2
		21 days	SC	11.9	12.2
(3)	Rat	7-8 weeks	SC; IV	5.0	5.0
(4)	[illegible]	7-9 years	IV	5.0	5.0

Comments

(1) & (2) Main toxic symptoms were a [illegible] or disappearance of spontaneous activity in 14 & 21-day-old animals, jumping & convulsions associated with meningorrhigia found at autopsy; majority of deaths occurred within 5 hrs after injection. LD50 values were lower at 3 & 14 days than at 21 days.

(3) Single dose of 5g/kg given. Mild renal damage (pale tubule cells, tubules dilated and/or containing cellular debris) was observed in [illegible] rats.

(4) Single dose of 5g/kg given to 2/se . Soft feces occurred in 2 M. Microscopically, diffuse acute low grade fatty change in liver parenchymal cells in both M; males unaffected. This finding may possibly be [illegible].

Subacute Toxicity Studies

1. [illegible] (Report [illegible])

A report of this study was previously reviewed by D. James (Original Submission date, [illegible]; Vol. 10,257, pharmacology review dated 5/[illegible]). This study was said to be invalid by the sponsor because standard operating procedures were not maintained, in that the temp. of the animal room reached extremely high levels (up to 29[illegible]). The sponsor indicated that this rendered interpretation difficult, but the results were recorded and presented so that they may be compared to a second experiment (Report [illegible]) in which good environmental control was sustained and from which reasonable conclusions may be drawn. Both Dr. James and I agree with the applicant that the results are extremely difficult to interpret /evaluate. Nevertheless, the highlights of this study as discussed by the applicant are summarized below for the record.

Species & Route: Hooded rats (PVG Strain) were treated daily with CFT SC as [illegible]...

Study section	Group No.	Dose g/kg/day	No. of animals of each sex
Experiment 294	1	Control (saline)	10
189/190 days	2	0.1	10
treatment	3	0.5	10
Autopsy on	4	2.5	10
following day			
Experiment 295	1	Control (saline)	5
Treated as above. Females autopsied on following day, males autopsied after 2 week recovery period	2	2.5	5

Findings

[illegible] were similar between treated and control groups at the end of treatment. Autopsy showed extensive centrilobular liver necrosis and, in some, a myocardial myocardial fibrosis of the left ventricle.

[illegible] retardation in the health of these animals was associated with the observed abnormally high environmental temperature. [illegible] Body weights [illegible] were comparable in good health [illegible] the effects were exacerbated by the blood & urine sampling [illegible] Quality was 1, 2, 3 & 5 in Expt. 294 only.

Effects of Treatment: Noteworthy changes were listed as follows:

Observations	Dose Levels
Clinical Signs	
diarrhea	2.5g/kg
reactions at the injection site	2.5g/kg
Body Weight	
reduced wt gain	2.5g/kg (M only)
Hematology	
mild regenerative, hypochromic macrocytic anemia	2.5g/kg
↓ in reticulocyte count	0.1g/kg (DR)
↓ in total leucocyte count	2.5g/kg
↓ in platelet count	2.5g/kg
slight ↓ in serum iron or iron binding capacity	2.5g/kg (M)
Coombs' test	2.5g/kg (Slightly positive results also found for 1 or 2 animals at 0.1 & 0.5g/kg.)
Clinical Chemistry	
slight to mod. ↑ in serum alkaline phosphatase	0.1g/kg (DR)
↑ in serum transaminase occurring in individuals particularly at week 4 or 8	2.5g/kg
otherwise ↑ serum transaminases	0.1g/kg or more
slight ↓ in serum potassium	2.5g/kg
↑ in urea nitrogen	2.5g/kg (Not seen in Expt 295)
Reduced serum total protein	0.1g/kg (Not " " " "; not DR.)
↑ in serum cholesterol	0.1gm/kg (DR; F more affected)
Water Intake & Urinalysis	
↑ in water intake & urine output; ↓ in urine specific gravity	2.5g/kg
↑ in urinary protein output	0.5g/kg (M more affected)
Organ Weights	
↑ in liver weight	0.1g/kg (DR)
↑ in kidney weight	0.5g/kg
↑ in spleen weight	2.5g/kg
↓ in brain & pituitary weights	2.5g/kg
↓ in heart & lung weights	2.5g/kg (M only)
↓ in uterus weight	2.5g/kg
Gross & Histopathology	
Inflammation and or hemorrhage at injection site	0.5g/kg (moderate 2.5g/kg (severe)
Liver damage	2.5g/kg
Myocardial fibrosis	2.5g/kg (seen in 1 M)
Kidney tubular damage	2.5g/kg
↑ erythropoiesis in spleen	2.5g/kg

Microscopy (For details, see the applicant's report, Vol. 5C, pp. 25-26.)

Liver damage consisted of extensive centrilobular necrosis, hepatic cell vacuolation and hemosiderin deposition present in the F1 rats at Wks 2-12. In the animals examined after 27 wks treatment, a few necrotic cells were present in a minority of animals and cell vacuolation was observed in 5/10 M. A little fibrosis around the central vein was observed in many animals.

Kidney tubular damage consisted of casts and debris and basophilic epithelium in some animals. All animals treated with 2.5g/kg showed an increased no. of eosinophilic droplets in the cytoplasm of proximal convoluted tubule cells. No effects were apparent after the 3-wk recovery period. At 0.1 & 0.5 g, the only change seen was a slight excess of lymphocytes in portal tracts of 3 rats at each dose level.

Applicant's Conclusion:

The only findings clearly of pathological significance were mild reversible renal changes and hepatic and myocardial necrosis in rats given 2.5g/kg. The renal changes were expected and do not suggest any undue hazard in clinical use. The hepatic and myocardial changes were unexpected since no such changes were seen in a previous test at dosages more than three times larger. Abnormally high environmental temperature may have been the main factor in this effect.

The other changes noted in this study, though not without significance, were mainly attributable to the haemorrhage and acute and chronic inflammatory reaction at the injection sites. At 0.1&0.5g/kg there was little difference from controls, an occasional increase in reticulocyte count being the only clinical change noted. 0.5g/kg had moderate effects and produced a slight anaemia by Week 2 which was fully compensated thereafter by a mild reticulocytosis. At 2.5g/kg the effects were severe, particularly in males. At this dose the anaemia was not fully compensated though there was increased splenic erythropoiesis and considerable splenic haemosiderin; increase mean cell volume reflected the increased proportion of circulating reticulocytes, while slight decreases of mean cell haemoglobin concentration are unexplained. The results do not suggest an autoimmune haemolysis and although the incidence of positive Coombs' test results was dose related it did not correlate in individuals with the degree of anaemia. The results are consistent with a blood loss of the extent observed at the injection sites. The leucocytosis and thrombocytosis at this stage is probably in the inflammatory reaction, and hyperkalemia may also be a result of tissue damage. The haematological changes completely reversible during the three week recovery period.

2. Rat - 28 Weeks - SC: (Report WPT/82/0004)

Methods: Hooded rats (PVC strain) were treated SC with CFT as illustrated

Study sub-division	Grp N	Dose g/kg/day	No. of animals of each sex	Duration of dosing (days)
R10006 28 weeks treatment followed by autopsy	1	Control (saline)	10	196-199
	2	0.1	10	
	3	0.3	10	
	4	0.9	10	
	5*	2.7	10	
*Electron microscopy performed on kidneys of 3 rats				
R10006A 28 weeks treatment followed by 59 day recovery period before autopsy	1	Control (saline)	5	196
	4	0.9	5	
	5	2.7	5	
Microscopic examination limited to liver, kidney & duodenum of group 5				
R10006B Absorption study after 29 weeks treatment and platelet aggregation study after 33 weeks treatment. No autopsy	1	Control (saline)	5	233-234
	2	0.1	5	
	3	0.3	5	
	4	0.9	5	
	5	2.7	5	

Results: Absorption Study: Plasma levels of CFT were dose-related and measurable at 15-45'.

Mortality: One gp 5 M rat was killed and one gp 4 F rat died. The M rat was killed on day 95 for histological investigations of hepatotoxicity suggested by increased enzyme levels and slightly lengthened clotting time in blood obtained on day 88. However, blood samples taken at autopsy showed none of these abnormalities. Post-mortem studies revealed a slightly enlarged spleen with evidence of erythropoiesis and a pale slightly mottled liver with evidence of fibroplasia. The F rat at autopsy showed congestion of the lung, thymus, liver & kidney.

Clinical Signs: Group 5: Loose feces, loss of condition (rough stick coat, dirty tail, thickning of skin, ↓ aggressiveness) and lethargy [illegible].

Body Weight: D in gp 5 M (infrequently seen in gp 3 M) during dosing; also seen in gp 4 & 5 recovery rats; subsequently gp 5 recovery rats showed good improvement, but not those of gp 4.

Food Consumed; Ophthalmoscopy; Hearing Test: No ORE

Hematology; Clinical Chemistry; Urinalysis; Organ Wts:

Note:

a) Statistically sig. results of possible biological importance are illustrated in Table 2, pages 12a & 12b. Numerical results are expressed as a proportion of the control mean.

b) Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum alkaline phosphatase all showed SS differences reflected by lower values among treated gps 4 & 5 CF controls; however, individual transient rises among the dec. values were also noted.

c) M of gp 5 showed a SS inc. in rel. lung Wt. Also seen in M & F recovery rats of gp 5, but this was attributed to low control values.

d) Water Intake: Variations encountered, but water intake generally higher for gps 4 & 5 CF controls.

e) Hematology: Mild, regenerative hypochromic, macrocytic anemia (gp 5; less extent in gp 4); leukocytosis (gp 5); I thrombotest time (gp 5 F); I platelet count (gp 4 M & gp 5). Inc. platelet sensitivity to ADP (gp 5 F). These were considered to be a consequence of hemorrhage inflammation at the injection site.

Pathology

a) Drug-related findings (also dose-related) of pathological sig. were:

- Mild fibrosis around the central veins & some portal tracts of the liver. A large proportion of gp 5 was affected (F M). Only 2 F rats in gp 4 showed very mild changes as such, and none were seen in gps 2 & 3. All animals in gp 5 showed hepatic change to an extent similar to that in the main study.

- Hemorrhage at the injection site: "Histologically there was hemorrhage, fibroplasia with or without inflammation, heavy hemosiderin deposition and in some instances, granulation tissue formation. The severity of the changes differed from one rat to another but it was only the two highest dose groups that were affected. Several tissues were involved in the changes directly and indirectly caused by the subcutaneous injections and subsequent hemorrhage. Anemia was noted by hematological examination and was confirmed by evidence of hemopoiesis in the spleen. Hemosiderin

Table 3

Statistically Significant Results
of Possible Biological Importance - Study #2

		R10005				R10005A			
		End of treatment period				End of treatment period		End of recovery period	
Dose (g/kg/day)		0.1	0.3	0.9	2.7	0.9	2.7	0.9	2.7
Group no.		2	3	4	5	4	5	4	5
Body weight	M	1	0.9*	1	0.8*	0.9*	0.8*	0.9*	0.8*
	F	1	1	1	1.1	1	1.1*	1	1
Haemoglobin	M	1	1	0.9*	0.7*	0.9*	0.7*	1	1*
	F	1	1	0.9	0.8*	1	0.7*	1	0.9*
Packed cell volume	M	1	1	0.9*	0.7*	0.9*	0.8*	1	1
	F	1	1	1	0.8*	1	0.7*	1	0.9*
Erythrocytes	M	0.9	1	0.9*	0.8*	1	0.8*	1	1
	F	1	1	1	0.8*	1	0.8*	1	0.9*
Reticulocytes	M	1.1	1	1.6	5.8*	1.5	4.9*	0.6	0.9
	F	1	1.2	1.2	5.3*	1	4.8*	1.6	2
Mean cell fragility#	M			1	0.9*			1	1*
	F			1	0.9*			1	1
Leucocytes	M	0.8	0.9	0.9	1.7*	0.9	1.2	0.9	0.9
	F	0.9	0.9	0.8	1.3	0.9	1.9*	0.9	0.9
Thromboplast	M	1	1	0.9*	0.9*	0.9*	0.8*	1.1	1.1
	F	1	1	1	0.9	0.9*	0.9*	0.9	1
Prothrombin time#	M	1	1	1	1			1	1
	F	1	1	1	1.1*			1	1
Platelets	M	1.1	1.1	1.5*	2.3*	1.1	1.8*	1.1	1.1
	F	0.9	0.9	1	1.5*	2	2	1	1.1
Marrow M/E ratio#	M		1.1	0.9	0.6*			0.9	0.9*
	F			1	0.7*			0.9	0.8

Table 2 (Cont.)

Statistically Significant Results
of Possible Biological Importance - Study #2

		Rabbit				Rat			
		End of treatment period				End of treatment period		End of recovery period	
Dose (g/kg/day)		0.1	0.3	0.9	2.7	0.9	2.7	0.9	2.7
Group no.		2	3	4	5	4	5	4	5
Serum/plasma albumin #	M	1	1	0.8*	0.7*			1	1
	F	1	1	1	0.8*			1	1
Serum cholesterol	M	1.2	1.1	1.2	1.1	1.2*	0.9	a	a
	F	1.3	1.4*	1.6*	1.5*	1.7*	1.4*	a	a
Serum/plasma triglycerides #	M	0.7*	0.6*	0.7*	0.7*			0.7*	0.8*
	F	0.8	0.8*	0.9	0.8			1.3*	1
Serum bilirubin	M	1.5	1.7	2.1*	3*	1.6*	2.3*	2.3	0.8
	F	1.2	1.4	1.4	2.5*	1.1	1.5*	3.8*	1.1* b
Urine volume	M	1.2	1	1.1	1.7*	1.0	1.7	1	1.4
	F	1	1.8	2.0	2.3*	0.5	0.9	0.6*	0.6*
Urine protein output	M	1	1	1.2	1.7*	1.2	1.9*	0.8	1.4*
	F	1.1	1.5	1.8	2.4*	0.6	1.2	0.7*	0.7*
Liver weight (relative) #	M	0.9	0.9	1	1.3*			0.9*	1.2*
	F	1	1.1	1.3*	1.4*			1.1*	1.1*
Kidney weight (relative) #	M	1.1	1.1*	1.2*	1.4*			1	1.2*
	F	1.1*	1.1*	1.2*	1.3*			1	1
Adrenal weight #	M	1.1	1	0.9	1.1			0.9	0.9
	F	1.1	1	1.2	1.4*			1.2	1.5*
Spleen weight (relative) #	M	0.9	0.9	1	1.7*			1	1.3*
	F	1	1	1	1.6*			1.1	1.2*

* Group mean significantly different from that of the corresponding control group ($P<0.05$)

\# Measured at end of treatment or recovery period only

a Values not available

b High values after recovery reflect unusually low control mean.

deposition was observed in hepatic phagocytic cells and occasionally within hepatocytes in a large proportion of the rats in Groups 4 and 5, and was more marked in the females. All the males, in Group 5 only, had hemosiderin present in the lamina propria of the duodenum. No reduction of hemosiderin deposition at either site was seen in the recovery group 5 animals."

b. Other findings which were dose-related and not considered of pathological significance by the applicant were:

- Edema of the salivary gland in all dosed gps plus 1 control rat; however, no microscopic abnormalities were noted.

-"The second feature in this category was the presence of eosinophilic droplets in the cytoplasm of some proximal convoluted tubules. These occurred in Group 5 and to a lesser extent in Group 4. The droplets were not seen in the kidneys from animals of recovery group 5. Evidence from hematoxylin and eosin stained sections indicated that the droplets were at least partly protein in nature. In addition, coarse brown granular aggregates were seen in the cytoplasm and lumen of a very few proximal convoluted tubules. This finding was confined to female rats, the majority of Group 5 and some of Group 4 being affected. The granules gave a negative staining reaction for iron and were still present in the kidneys of the female recovery Group 5. No abnormalities were detected in the glomeruli by any of three light microscopy techiques employed or by electron microscopy."

Conclusion of Applicant: The only changes of pathological significance were those in the liver at levels of 0.9 g/kg or more.

Comments: See discussion of applicant, pp.33-36 (Vol. 58). The results of this study would indicate that 0.3 g/kg of CFT was relatively well-tolerated in this study.

3. Dog - IV - 28 Weeks: (MPT 182026)

Methods: Beagle dogs (16-27 weeks old) were treated IV with CFT as illustrated below:

Experiment division	Group No.	Dose (mg/kg/day)	No. of dogs of each sex
26 weeks treatment followed by autopsy	1	Control - saline	4
	2	85	4
	3	255	4
	4	595	4
	5	850	4
26 weeks treatment followed by a recovery period of 3 weeks before autopsy	6	Control - saline	2
	7	595	2

*Analysis of plasma samples taken 24 hrs after dosing (days 1, 28, 168) showed that the conc'n of CFT in all dosed gps was less than 1 ug CFT/ml.
**Electron microscopy was performed on kidney proximal tubule cells from dogs of gp 5.

Results

Clinical Signs; Mortality: There was salivation & vomiting associated with injection in a dose-related manner. Two dogs died (gp 2 M & gp 3 F); however, death was not DR.

Body Wt Gain; Ophthalmology; EKG: There were no DR findings. There was an inc. in HR (SS) in gp 4 & 5 vs CF controls; however, this was thought to reflect normal excitement; also no effect was present in gp 7.

Urinalysis: There were no DR findings of toxicological significance.

Hematology: Occasional variations were encountered (e.g., prolongation of PTT, gps 4 & 5) sometimes being SS; however, these were more likely to have arisen by chance rather than being DR [see p. 13 in applicant's report (AR) & Tables III-V].

Clinical Chemistry: (Days 1, 30, 45, 87, 143, 180 & 210) The following changes appeared to be DR according to the applicant:

- Plasma alanine aminotransferase: There was suppression of the normal inc. (CF controls) in activity that was dose-related in all M gps (SS in gps 4 & 5); however, recovery was seen on cessation of treatment. In F there were no clear dose-related changes; however, in gps 3 & 5 there were lower values (SS) on several occasions, but gp 7 showed recovery on cessation of treatment.

- Plasma aspartate aminotransferase: Some reductions in treatment gps were observed (not dose-related); however, differences from controls were rarely SS.

- Plasma & Serum Protein: Slight but SS incs. were noted in gps 5 & 7 (" & F) and gp 4 (") on several occasions; however, 2 wks after cessation of treatment, gp 7 incs. were not SS different from controls.

- Plasma albumin: Tended to be slightly higher than controls, though this was sig. only for gp 4 M on day 10 & gp 7 F on day 45.

- Serum protein electrophoresis: Carried out only at the end of treatment (and during recovery). In all antibiotic treated gps gamma-globulin was reduced (0.5-0.7x control). This change was proportional to dosage in F but not in M, and was still evident 2 wks after cessation of treatment. The B-globulin fraction was also slightly reduced in gp 5 M.

- Plasma cholesterol: On day 45 and subsequently during treatment mean total cholesterol for all antibiotic treated gps was higher than control, though the differences were seldom SS. Gps 2, 3 & 4 showed a dose-related inc., particularly in F, but gp 5 values showed a cessation (M) or a reversal (F) of this trend. Results for gps 6 & 7 showed no clear evidence of recovery after cessation of treatment.

Urinalysis: No consistent treatment-related changes were observed.

Organ Weights: "The only organ showing a clearly treatment-related change was the liver. This was markedly increased in Group 5 females (relative weight 1.6 times control, P 0.05) and possibly also slightly increased in Groups 3 & 4 female and Group 5 male (1.1 to 1.2 times control, P 0.05). Three weeks after cessation of treatment liver weight for both sexes in Group 7 was 1.2 times control (P 0.05)."

- Comments: In Table XI of the AR, the kidney wt (abs. & rel.) of gps 5 (" & F) were slightly higher than controls, but not SS.

Pathology & Electronmicroscpy: The only DR findings were in the kidney. Occasional acidophilic droplets occur naturally in the cytoplasm of the proximal convoluted tubular cells of the dog. However, in the present study it was observed that the numbers of such droplets tended to inc. at the higher levels of treatment (dose-related in gps 3, 4 & 5) and were generally larger and of less regular shape. The no. of dogs in each gp in which this change was noted was as follows:

	End of treatment period					End of recovery period	
Group (mg/kg/day)	1 -	2 [illegible]	3 [illegible]	4 - [illegible]	5 [illegible]	6 -	7 [illegible]
No. of dogs affected	0	0	2	2	4	0	1*
No. of dogs examined	3	3	-	3	4	-	1

*Recovery dog still affected 3 wks later.

Special staining indicated that these droplets were protein and also contained some CFT. Electron microscopic exam of these droplets indicated that they were heterolysosomes. Also, electronmicroscopy revealed no ultrastructural DR damage. The applicant indicated that the proximal tubular cells were dealing with the droplets by normal cellular processes.

Comments:

a) More recently this reviewer has read about similar renal heterolysosomes as occurring in animals treated with other cephalosporins (see [illegible] 22.171, pharmacology review dated 8/9/83) and this did not constitute a pathological change.

b) See also discussion of applicant, illustrated below.

The several treatment-related changes observed in this study were generally absent at the smallest dosage (35 mg/kg/day) and even at the largest dosage (350 mg/kg/day) had no apparent pathological significance. The only clearly adverse effect produced by ceftazidime was vomiting on administration. This is considered to be a non-specific physiological response to a massive intravenous bolus of foreign chemical. Of the other changes noted, decreased serum gamma-globulin probably reflects antibiotic related reduction of immunogenic stimulus, particularly as there was little difference in response between dosage groups. The presence of droplets containing ceftazidime in the renal tubular epithelium was examined in some detail because of the reputation of cephalosporins as nephrotoxins. The demonstration, by special stains and electron microscopy, that these were heterolysosomes in that no injury to the tubular cell or glomerulus was involved, is consistent with the absence of any evidence of renal damage or malfunction in urine analyses.

The explanation for the suppression of the normal age related increases in plasma aminotransferase activities, and for the increased plasma cholesterol and total protein, is uncertain, but the changes suggest a gradual metabolic alteration and may well be associated with the mild, benign hepatomegaly. They were generally not apparent until Day 45, which might explain their absence after 28 days treatment in the previous one month study (Label-Edwards et al. 1980). However, hepatomegaly was observed at the end of that study, though only at the largest dosage (540 mg/kg day). The absence in the present study of minor changes seen in the one month study, i.e. increased triglycerides in males and decreased blood glucose in females, is also unexplained.

After three weeks recovery in dogs given 595mg/kg/day, the reduction of serum gamma globulin remained unchanged but the other differences in blood biochemistry and in liver weight had lessened and the effect on acidophilic droplets in the kidney was less noticeable, indicating a gradual regression."

Applicant's Conclusion: The above-mentioned various changes discussed had no pathological significance.

Reproduction: Segment II Rabbit Study - I"

Animals: Female Dutch rabbits

Groups: 5 groups: Groups 1-4, at least 12 pregnant F/gp; Group 5, only 6 (because of maternal toxicity).

Dosage & Route: Groups 1-5, respectively, received saline, 25, 50, 100 & 200 mg/kg of [illegible] I" from days 6-18 of pregnancy and were killed on day 29 of pregnancy.

Results

Observation of Dams: Many treated dams died or were killed because of poor health or because they aborted their fetuses. The incidence of death was not dose-related and was highest in Group 2 (see table below). Some of the rabbits had diarrhea and were emaciated before death. Of those that survived the experiment, some had diarrhea, but the majority remained in good health.

Group	Number mated	Number found dead	Number killed before day 29 of pregnancy	Number surviving	
				Not pregnant	Pregnant
1	29	1	1	6*	17
2	29	3	-	1	15
3	27	1	1	3	12
4	29	6	2	5	12
5	12	3	1	1	6

Most of the pathology observed was reported to have been naturally occurring and no toxic effects were found on microscopic exam. of selected organs from rabbits given CPT with the exception of one rabbit in gp 2 which had evidence of mild bowel irritation. In other rabbits, the bowel was [illegible] normal or was not satisfyed for interpretation. Local irritancy was observed in a minority of the IV injection sites. The incidence of [illegible] was thought to be [illegible] many cases due to disturbance of the intestinal flora. CPT was found in the GI tract of rabbits that died or were killed.

Body Weight: Maternal body wt in the gp given 60 mg/kg was less (SS) than in controls from day 21 on, and also in the MD gp from day 21 on. All gps given CPT showed some evidence of a D in body wt gain OF controls during the first weeks of dosing.

Hematology; Clinical Chemistry: No ND findings.

Observation of Uterine Contents: See Table 3 below.

The number of implantation sites was unaffected by treatment. The number of live fetuses, and the live litter wt, mean live fetus wt and mean placenta wt were decreased in rabbits given CPT; and the no. of resorption sites was increased. The effects were dose-related, but did not reach statis. sig. ($P < 0.05$). There were 2 dead fetuses; one in gp [illegible] and one in gp 4.

TABLE 3 OBSERVATIONS IN THE CAESAREAN : MEAN RESULTS

OBSERVATION	GP1	GP2	GP3	GP4	GP5	
IMPLANTATIONS	[illegible]	8	8	8	8	
RESORPTIONS	[illegible]	[illegible]	2	2	4	*
LIVE FOETUSES	6	5	4	4	3	
LIVE LITTER WEIGHT G.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
MEAN LITTER MEAN LIVE FOETUS WT. G	[illegible]	39.8	38.6	25.9	24.5	
MEAN LITTER MEAN PLACENTA WT. G	3.69	3.66	3.66	3.37	3.31	

PROPORTION OF LITTER WITH BONE VARIANTS (%)

STERNUM	1	1	3	1	1	N
SKULL	1	1	0	1	1	N
FORELIMBS	2	2	2	5	1	N
HINDLIMBS	1	1	1	3	0	N
TOTAL	4	13	3	8	11	N

PROPORTION OF LITTER WITH BONE VARIANTS (%)

	56	44	67	54	33	T

PROPORTION OF LITTER WITH BONE ABNORMALITIES (%)

	1	13	2	11	2	N

T = Observations transformed for analysis.
N = No statistical analysis performed.

Observation of Fetuses: Three fetuses (see AR page 23, vol. 69) from one litter of 5 in the 25 mg/kg gp had gross external malformations. Apart from 1 dead fetus (control gp) that had flexed forepaws, no other external abnormalities were seen.

Soft Tissue Abnormalities: No DR findings reported.

Skeletons:

a) Maturity: See also Table 3 above. Although none of the measurements were analysed statistically a comparison of the gp means did not indicate that treatment had any adverse effect on maturation.

Comments: As can be seen in Table 3, the drug-treated gps showed a higher incidence in bone immaturity. However, in the absence of a dose response relationship, no conclusions can be drawn.

~~b) Variants: No DR findings~~

c) Abnormalities: No apparent DR effects (HD control).

Evaluation of Teriflunomide: IM doses of 25-200 mg/kg of SPT produced [illegible] embryotoxicity, but no teratogenicity.

Embryotoxicity: See Table 4 below.

Table 4

Long-term Toxicity Studies with Cefixime & Related Antibiotics

1. Drug of Class

Rat (M/F)	Drug(s)	Dose g/kg	Route	Duration
(30)	*Saline (CFT**)	(5ml)	SC	SD***
	*CFT	10	"	"
	*CEP	10	"	"
	Probenecid	0.1g	PO	"

*Also saline, CFT or CEP given after probenicid
**Control
***Single Dose

Comments: Kidneys examined microscopically (Mic) 48 hrs later. CFT alone was very slightly nephrotoxic (10% of mice with proximal tubular necrosis (PTN)). Pretreatment with Probenecid had no effect on CFT. CEP alone was severely nephrotoxic (100% of mice with PTN); however, effect was prevented by treatment with Probenecid.

2. Cephalosporin (sex)

Rat (M)	Drug(s)	Dose g/kg	Route	Duration
(6)	*Saline (C)	(5ml)	SC	SD
	CFT	4	"	"
	CEF	4	"	"

Comments: Kidneys examined (Mic) 48 hrs post-dosing. Both CFT & CEF produced similar results, i.e., a moderate (outer cortical region not affected) degree of PTN in 100% of the animals of each gp.

3. Cephalosporin (sex)

Rat (M)	Drug(s)	Dose g/kg	Route	Duration
(5)	a Saline	(5ml)	SC	SD
	b CFT	4	"	"
	c CEP	2	"	"
	a, b or c + Furosemide	0.1	"	"
	a, b or c + Probenicid	0.1	PO	"

Comments: Kidneys examined as above. Given alone, both CFT & CEP produced a similar degree of PTN (100% of animals). Furosemide given 1 hr previously enhanced the degree of necrosis with CEP but not with CFT. Pretreatment with probenicid produced no sig. modification of the [illegible] by CEP (compared to study 2 in the mouse) nor by that of CFT (only slightly decreased).

4.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Rat (M)	Saline (1 gp)	10	SC	SD
(5)	Genta (1 gps)	0.010	"	"
	CFT (1 gps)	4	"	"

Comments: Rats were given Genta alone & kidneys examined (Mic) at 24, 48 & 72 hrs. Also rats were given CFT alone & kidneys examined (Mic) 48 hrs after CFT & at the same intervals after Genta (i.e., 24, 48 & 72 hrs). As expected, Genta alone had no effect after 2-3 days, since an effect would normally be evident after 5-10 days. CFT produced PTN (100% of animals) & the nature & degree of PTN was unaffected by Genta.

5.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Mouse (F) (10)	CFT	10	SC	SD
	CEP	1.1	"	"
Rat (F) (5)	CFT	4	"	"
	CEP	2	"	"

Comments: 1, 2, 3 & 7 days after dosing, 1 gp of each species had their kidneys examined (Mic). Mice: Dosed with CFT; the only change was a small amt of proximal tubular necrosis after 2 days. No abnormality was present after 3 days. CEP produced extensive necrosis by 1 day, regeneration was predominant at 3 days & nearly complete by 7 days. CFT affected only the inner cortex, while CEP affected the outer cortex. Rats: Given either antibiotic, after 1 day there was exfoliation in proximal tubules & after 2 days extensive necrosis. Regeneration was predominant at 3 days & nearly complete by 7 days. Rats given CFT showed more necrosis, but recovered more quickly than those given CEP. Both antibiotics affected only the inner cortex.

6.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Rabbit (F) (4)	Saline	4 ml	SC	SD
	CEP	0.2	"	"
	CFT	0.4, 0.8	"	"
	CEZ	0.4, 0.8	"	"

Comments: The effect on the kidney 48 hrs after dosing was assessed by measurement of plasma urea & creatinine; also by gluconeogenesis & uptake of para-aminohippurate & tetraethylammonium in renal cortical slices; and by microscopic exam (tubular degeneration ranging from a few cells exhibiting apoptosis to complete necrosis, with or without associated calcification). CFT 400 & 800mg/kg: No abnormality in any of the parameters of renal damage. CEZ 400mg/kg: Slight effect, ↓↓ only in [illegible] plasma urea. Histological changes were seen in 2 rabbits [illegible] on plasma urea in one of these. CEP 800mg/kg & CEZ 800mg/kg: Marked accumulation of plasma urea & creatinine, cation-anion transport, gluconeogenesis & histology.

Conclusions: CFT had no adverse effects at 200 & 800mg/kg. CEZ was mildly nephrotoxic at 400mg/kg. Both CEZ at 800 & CEP at 800mg/kg produced moderate to severe nephrotoxicity.

7. Species (sex) (n/gp)

	Drug(s)	Dose g/kg	Route	Duration
Rat (M) (8)	Saline	10ml	SC	10 days
	CFT	4	"	" "
	Genta	0.035	"	" "
	Amikacin	0.25	"	" "
	Tobramycin	0.06	"	" "
	Genta + CFT	0.35 + 4	"	" "
	Amikacin + CFT	0.25 + 4	"	" "
	Tobramycin + CFT	0.06 + 4	"	" "

Comments: Animals were killed 24 hrs & kidneys examined Mic. Prox. tubular regeneration occurred with CFT alone in the inner cortex which was consistent with the occurrence of necrosis during the first 24-48 hrs of the study. The aminoglycosides (AG) also caused necrosis & consequent regeneration (mainly in outer cortex); however, recent necrosis was a common feature. Combined treatment of CFT & AG ameliorated their toxicity in that no recent necrosis was observed & less regeneration of the outer cortex was noted. Inner cortical changes, however, were similar to those given CFT alone.

Conclusion: CFT at nephrotoxic doses during a 10-day regimen protected rats against the nephrotoxic effects of AG.

8. Species (sex) (n/gp)

	Drug(s)	Dose g/kg	Route	Duration
Rat (M) (10)	Saline	10ml	SC	10 days
	CFT	4	"	" "

Comments: Renal damage was assessed during the 10-day period by measurement of urine:volume, specific gravity, protein conc'n & output*, gamma glutamyl transferase activity & output*, & epithelial cell count & output*. (*Output of 16 hrs/day) Also serum urea nitrogen was estimated 24 hrs after the last dose when the rats were killed & their kidneys examined microscopically.

Daily dosing with CFT initially produced signs of kidney damage with inc. urinary output of enzymes, protein & epithelial cells. The inc. were maximal on day 2; however, despite the continued treatment, there then followed a progressive return to normal values. At the end of 10 days treatment, kidney histology showed regenerating tubular epithelium in the inner cortex of 7/10 rats & normal cells in 3/10 rats. The same 3 rats had shown less evidence of initial damage, with no inc. in urine protein [illegible] transferase output & only a small inc. in alkaline phosphatase output. The applicant indicated that similar results were [illegible] ref. to Fitzel-Edwards et al, Proc. Roy. Soc. Med. 70, 1977, Supplement 8, 41-49). However, CFT produced somewhat larger incs. in urinary output of protein, alkaline phosphatase & gamma-glutamyl

transferase & more histological evidence of kidney damage than cefuroxime given for 10 days at the same dosage.

Table 5

Local Irritation

1.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Rabbit (M) (weanlings) (3)	CFT	0.2ml (25% w/v sol'n)	IM	SD
	BP	0.2ml (20% w/v sol'n)	IM	SD

Comments: Rabbits were dosed IM with CFT or with benzyl penicillin used as a control, into the left & right sacrospinalis muscles, respectively. The animals were killed 2, 7 & 14 days after dosing & the muscle examined Mic. Both drugs produced small areas of muscle necrosis which by 7 days were being healed by repair & muscle regeneration. By 14 days the healing process was virtually complete. It was concluded that CFT was mildly irritating to immature rabbit muscle & healing of the muscle was rapid.

2.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Rabbit (M) (4)	NaCl (0.9% w/v)	0.1ml	Subconjunctively in rt. eye, once/ day for 3 days performed under anesthesia.	
	CFT (10% w/v)	0.1ml		

Comments: Eyes were scored (Draize, 1944); left eye compared to rt) at 10-120' post-dosing & rabbits were killed on the day after the last dose & histology on ocular tissues was performed. No sig. local irritation by CFT was detected by repeated clinical testing up to 2 hrs post-dosing, nor by histologic exam of eyelids, ocular muscle, lachrymal gland, eyeball & optic nerve. It was concluded that CFT was not likely to cause local irritation if injected subconjunctivally as a 10% sol'n at therapeutic doses.

3.

Species (sex) (#/gp)	Drug(s)	Dose g/kg	Route	Duration
Rabbit (M/F) (2/sex)	NaCl (0.9% w/v)	0.1ml	Instilled into the conjunctival sac of the left eye	
	CFT 0.625% w/v	0.1ml	"	
	[illegible] w/v	"		
	30% w/v	"		

Comments: After each instillation the left eye was compared to the rt. eye at 30, 60 & 150' (as in above study). CFT caused no local irritation (score = zero) when 0.1ml was instilled into the rabbit eye at conc'ns up to 10% w/v.

4. Species (sex) (#/gp) | Drug(s) | Dose g/kg | Route | Duration

Animals were given a single IP dose of dialysis fluid (3ml/100 g body wt) containing CFT or CEZ at a conc'n of 0.015, 0.05 or 0.15% w/v.

Comments: Irritancy was determined by examination (volume, mast cells, differential leukocyte count, etc.) of peritoneal washings collected 5-6 or 24-25 hrs after dosing & by histopathologic exam of the peritoneum. The dose vols. & conc'ns used were reported to be equivalent to the admin. of up to 2 litres of sol'n containing 3g CFT to a 70kg human. Neither drug caused any detectable irritation of the peritoneum in the animals tested. It was concluded that the proposed IP admin. of CFT to humans was not contraindicated by the results of this study.

5. Species (sex) (#/gp) | Drug(s) | Dose g/kg | Route | Duration

Rabbit (M) (1-3) | CFT Ampicillin Sodium (Ampi) & Genta at respective conc'ns of 5, 6 & 10% w/v in isotonic saline (control) were given intracisternally (single dose) under anesthesia to the animals. Doses were: CFT = 1.25, 2.5, 5, 10mg/kg; Genta = 1.13, 2.25, 4.5, 9, 18 & 36mg/kg; Ampi = 6 & 12mg/kg; rabbits were killed 4 days later, being examined each day.

Comments: CFT caused severe convulsions at 10mg/kg & moderate convulsions during the first 30' were seen in 1/4 rabbits given 5mg/kg. A mild transient inc. in response to stimuli was seen in 1/3 rabbits at 2.5mg/kg. At 1.25mg/kg there were no DRE. Ampi showed no DRE at 6mg/kg, but caused convulsions after a dose of 12mg/kg. Genta caused convulsions between 7' & 3 hrs after doses ranging from 4.5-36mg/kg. Some rabbits given doses ranging from 2.25-9 mg/kg showed signs of general muscle weakness & inactivity. There were no DRE at 1.13mg/kg. Analysis of the cerebrospinal fluid & microscopic exam of the brain, spinal cord & meninges revealed no evidence of any lesion that could be attributed to treatment with any of the antibiotics. The applicant concluded that intrathecal doses could be well-tolerated in humans at levels less than 1.5mg/kg.

6. Species (sex) (#/gp) | Drug(s) | Dose g/kg | Route | Duration

Rabbit | CFT (5% w/v), Thiopentone Sodium (5% w/v) & Sodium Chloride (isotonic) were injected once into the central ear artery of the rt. ear at a vol. of 0.5ml. Rabbits were killed 4 days later & during that time the ears were examined.

Comments: There was minimal tissue damage grossly & microscopically by CFT almost being comparable to the control saline gp. Thiopentone, however, exhibited severe tissue damage & necrosis. It was concluded that the accidental intraarterial injection of CFT in humans would be unlikely to lead to serious side effects.

Table 6

Mutagenicity & Immunology

Test System	Species (Route)	Dose
Micronucleus Test	Mouse (IP)	1 & 2.5 g/kg of CFT

Comments: Fresh & stored (25°C for 24 hrs) sol'ns (10% w/v & 25% w/v) of CFT were tested in 11 mice. In this test system neither CFT nor the pyridine generated through degradation of CFT during storage in sol'n induced a sig. inc. in detectable chromosome damage in mouse bone marrow cells. Cyclophosphamide gave positive results, thus validating the method used.

Immunological Studies: Volume #70, page 100-217. The reader is referred to the review of this Form 5 #50-578 by the microbilogist, Richard King, Ph.D.

Pyridine Toxicity

Background:

The FDA requested from the applicant based on information in the parent IND to assess the potential for pyridine causing toxicity when CFT is decomposed on storage. Pyridine affects the CNS & causes degeneration of the liver and kidneys.

According to the applicant, degradation of CFT for injection results in the formation of pyridine in both the dry blend and the constituted injection. Stability studies indicated that between 0.2% & 0.3% pyridine could be present after storage in the dry state for the period of the shelf life and that an inc. in pyridine content on the order of 0.7% could occur on storage in sol'n for 24 hrs at 25°C. The maximum amount of pyridine expected after such storage would be approx. 1%. Based on a maximum dose of 6g CFT/day and a maximum pyridine content of about 1%, the daily exposure would be 1mg/kg/day /60kg adult.

A literature survey was conducted on the toxicity of pyridine with special reference to the IV route (for details see Vol. 71D, references # 1-12) by the applicant. The animal data reviewed by the applicant indicated the following:

1. Pyridine has a low order of acute toxicity in all species studied; e.g., LD50 = 891 mg/kg in dogs dosed IV.

3. There are no facets of its pharmacological profile which suggest that low levels will have any biological activity, e.g., 2.5mg/kg given IV to cats had no effect on the cardiovascular system; effects were seen at 10mg/kg.

3. At "realistic" dose there is no indication that pyridine is mutagenic.

4. In a long-term study (Mason 1969), SC doses of up to [illegible]mg/kg were given twice/wk for 1 year and the animals observed for a further 6 months. No sig. toxicity or carcinogenicity was detected.

5. In a micronucleus test on fresh & stored ceftazidime (reviewed under mutagenicity), neither fresh nor stored CFT induced a sig. inc. in detectable chromosome damage.

Applicant's Conclusion: The animal data "strongly indicate" that the small amounts of pyridine which may be present in stored CFT are of no toxicological significance.

Comments:

1. Currently, NCI is conducting a carcinogenicity study (started in Feb. 1979) with pyridine. Also, in 1979, FDA considered Mason's carcinogenicity study to be inadequate by current standards & recommended that appropriate carcinogenicity, mutagenicity & teratogenicity testing of pyridine be carried out.

2. At this point in time, it is not unreasonable to accept the applicant's conclusion concerning the lack of potential toxicity by the small amounts of pyridine in stored CFT.

Evaluation Overview:

Fortaz™ (ceftazidime pentahydrate) is a broad spectrum cephalosporin antibiotic for parenteral administration. It is to be indicated in the treatment of infections due to susceptible strains of microorganisms designated in the package insert. The usual adult dose is 1g given 3x/day (IV, IM) and the maximum adult dose is 6 g/day (120mg/kg/day/50 kg adult). Lower doses are recommended in patients with impaired renal function. The recommended dose for neonates (0-4 wks old) is 30mg/kg IV every 12 hours and that for infants & children (1 month to 12 years) is 30-50mg/kg IV every 8 hours to a maximum dose of 6g/day (reserved for infections in immunocompromised or fibrocystic children).

The following is a preclinical overview giving highlights of the pharmacologic and toxicologic profile of ceftazidime. Comparisons of animal doses to the human dose is based on the proposed maximum human dose of 6g/day [illegible].

For [illegible] studies have been carried out in mice, rats, cats and [illegible]. [illegible] were used to study the possible effects of [illegible]. Rats and mice were treated SC with [illegible]g/kg and dogs were given [illegible], SC or [illegible]mg/kg IV. Only minor effects were seen in the mice,

and the normal behavior, body temperature and pupil diameter of the rats and dogs were not affected by the doses they received.

Cardiovascular, respiratory and autonomic nervous system responses were studied in anesthetized dogs and cats treated with up to 1000mg/kg IV. There were very minor responses in mean arterial BP, HR and respiration when cats received 1g/kg IV. These minor cardio-respiratory effects were probably a response to the large amount of material and the high level of electrolyte that the animals received. The injection of neurohumoral agents in cats and dogs showed no effects when 10-1000mg/kg of ceftazidime were given to the same animals IV. The nictitating membrane's response to preganglionic nerve stimulation in the cat did not seem to be affected to an important degree with 10-300mg/kg of ceftazidime. When the dose reached 1g/kg in these cats, there was some weak nicotinic or adrenoreceptor blockade noticeable because of a slight inhibition of contraction of the nictitating membrane, but this may have been a part of a mechanical problem.

Unanesthetized mice and rats, when given 4g/kg of ceftazidime SC had a slight inhibition of gastrointestinal propulsion. The resting tone or spontaneous contractions of the uterine smooth muscle from either pregnant or non-pregnant rats was not altered by 300-1000mg/kg doses of ceftazidime given IV.

Pharmacokinetic studies were carried out in mice, rats, rabbits, cats and dogs using ^{14}C-labeled or unlabeled ceftazidime and some of these studies were autoradiographic in nature. Ceftazidime was rapidly absorbed from muscle and subcutaneous tissues; e.g., radioactivity was detected in rat urine after 5 minutes of dosing with ^{14}C-labeled drug. Peak plasma levels in several species dosed parenterally were attained within 15 to 30 minutes and elimination was rapid; half-lives were mostly less than 1 hour, e.g., dogs dosed IM and rats dosed IV had elimination half-lives of between 45 to 50 minutes and 26 to 28 minutes, respectively. The primary route of excretion was via the kidney, while biliary excretion was almost negligible (e.g., within 4 to 5 hours after dosing in rats, less than 1% of the subcutaneously administered dose was excreted in the bile). Autoradiographic studies in rats also revealed that this drug was secreted by the gastric mucosa in the lumen of the stomach. Most metabolic studies indicated that ceftazidime hardly undergoes metabolic transformation and is primarily excluded unchanged in urine or bile (e.g., less than 0.1% of the administered dose is due to metabolites in the bile of rats dosed SC). Studies in pregnant rats and rabbits indicated that small amounts cross the placenta to reach the fetus. Autoradiography revealed that the fetal kidneys and bladder were more heavily labeled than other tissues.

Studies in lactating rats also revealed that small amounts of the drug are excreted in the milk. Ceftazidime at high doses (500mg/kg) but not at low doses (20mg/kg) in rats showed some minor inducing effect on hepatic microsomal enzymes.

Tissue distribution studies revealed that the liver and kidney had the highest amount of drug concentration (radioactivity) among the organs and tissues (about 2-3x the conc. of plasma). Ceftazidime did not bind to any appreciable extent (less than 10%) to plasma protein of animals or humans.

Mutagenicity studies have not been conducted with ceftazidime; however, results of mutagenicity studies [using S. typhimurium (Ames Assay), Saccharomyces cerevisiae or the Micronucleus Test in mice] indicated a lack of mutagenic potential. In a second Micronucleus Test in mice, both fresh and aged solutions (250 for 24 hours) solutions (5% w/v and 20% w/v) of ceftazidime were used. Neither ceftazidime nor the pyridine generated through degradation of ceftazidime during storage in solution were found to be mutagenic.

Local irritation studies were carried out in rats and rabbits. In rats injected IP with dialysis fluid (3ml/100g body weight) neither ceftazidime nor cefazolin at concentrations up to 0.15% w/v caused detectable irritation of the peritoneum. In mature and weanling rabbits, a 25% w/v solution of ceftazidime (1ml; 0.2ml, respectively) injected IM was found to be mildly irritating to the muscle; however, the lesion(s) produced were almost completely healed in 14 days. No significant local irritation to ocular tissues was produced when ceftazidime was injected (0.1ml, 10% w/v solution) subconjunctivally into the eye of the rabbit. Ceftazidime caused no local irritation when instilled into the rabbit eye at a dose of 0.1ml (30% w/v solution). Intracisternal doses of 1.25mg/kg of ceftazidime in rabbits were very well tolerated. Intraarterial injection of ceftazidime (0.5ml of a 25% w/v solution) caused minimal tissue damage, being almost comparable to the control saline.

Acute toxicity studies carried out in mice, rats, dogs and monkeys revealed that ceftazidime had a wide margin of safety in relation to the human dose. The LD_{50} values in mice, rats, dogs and monkeys dosed IV or SC were greater than 5g/kg (about 42x the human dose). Young mice and rats (3-21 days old) dosed IP or SC had LD_{50} values ranging from 4.6-12.2g/kg, the LD_{50} values being lower in 3 and 14 day-old animals than at 21 days of age. In one study the IV LD_{50} in male and female mature mice was determined to be 7100 and [illegible]mg/kg, respectively.

As with other beta lactam antibiotics, ceftazidime did not appear to be teratogenic when administered to rabbits by injection, but it did cause some degree of contact sensitivity in guinea pigs when applied topically to the skin.

Nephrotoxicity studies were carried out in rabbits, mice and rats. Single dose studies (IV, SC) in rabbits dosed with ceftazidime at levels up to [illegible]mg/kg revealed no nephrotoxicity. However, cefazolin was mildly nephrotoxic at 400mg/kg and both cefazolin and cephaloridine produced moderate to severe nephrotoxicity (proximal tubular degeneration and necrosis) at [illegible]mg/kg, respectively.

Single dose SC studies carried out in mice revealed the following: (a) No nephrotoxicity was encountered at 6g/kg, but 8 and 10g/kg caused inner cortical tubular necrosis; cephaloridine at 1.1g/kg produced a much greater nephrotoxic effect than that produced at 10g of ceftazidime. (b) Pretreatment [illegible] effect on the nephrotoxicity of ceftazidime (10g/kg) [illegible] reported that produced by cephaloridine (1.1g/kg). (c) Furosemide [illegible] potentiated its effect; [illegible] with ceftazidime [illegible] slightly potentiated its effect; [illegible] seen with cephaloridine.

Single dose SC studies carried out in rats reveal the following: (a) At 2g/kg of ceftazidime, there was exfoliation of the proximal tubular epithelial cells of the kidney, and at 4g/kg renal tubular necrosis occurred. Both ceftazidime and cefuroxime at 4g/kg produced similar effects, i.e., a moderate degree of proximal tubular necrosis. Pretreatment or concurrent treatment with probenecid and furosemide/gentamicin, respectively, did not affect the expected nephrotoxicity associated with 4g/kg of ceftazidime. However, furosemide, but not probenecid, markedly enhances the nephrotoxicty associated with 2g/kg of cephaloridine. (b) In repeat dose studies (10 days) using concommitant administration of ceftazidime with several aminoglycosides (including gentamicin) the cephalosporin (at nephrotoxic doses) appeared to protect the rat against the nephrotoxic effect of the aminoglycosides. In a 10-day study, renal damage (increased urinary output of enzyme, protein & epithelian cells) in rats seen with 4g/kg of ceftazidime was maximal on day 2. However, despite continued treatment, there then followed a progressive return to normal values.

Reproduction studies were carried out in mice, rats and rabbits. In a segment I reproduction and fertility study in male and female mice dosed SC with ceftazidime at levels of 0, 1.5, 3.25 & 6.5g/kg, there were no adverse effects on male or female fertility, although several high-dose dams died. In the F_1 generation, there was some increase in bone variation at the high-dose level. Also, there was a trend toward reduced pup weight during lactation in the high and mid-dose groups in the F_2 generation. The effects seen at the HD level have little relevance to the clinical situation, since this dose is about 54x the human dose and closely approximates the LD_{50} in female mice (6.3g/kg). In a segment III study in female rats dosed SC with ceftazidime at levels of 0, 0.1, 0.5 and 2.5g/kg, the mean weight of pups from the HD group were significantly less than that of controls; however, this was probably due to the toxic effect upon the GI tract of the dams, since they exhibited diarrhea.

Segment II studies were carried out in rabbits (IV) and mice (SC) dosed respectively with 0, 0.025, 0.15, 0.1 & 0.02g/kg, and 0, 1.5, 3.25 & 6.5 g/kg. In rabbits, there was maternal mortality and embryotoxicity (related to maternal toxicity) at all dose levels, but no teratogenicity. In mice, the drug was not embryotoxic or teratogenic; however, at the HD level, there was a significant increase in the number of rib variants; at the low dose, however, there was no effect on the skeleton of the animals.

Subacute toxicity studies of ca. 1, 3 & 6 months duration have been carried out in rats and dogs using the SC, IM or IV route of administration. The highlights of these studies are illustrated in Table 7 on the following page. For detailed summaries on these studies, the reader is referred to the previous pharmacology reviews in IND 10,257 by G. James (5/8/81), G. Debbas (1/7/81) and M. Carlin (9/17/82), and also to this NDA review under "Subacute Toxicity Studies".

Table 7
Subacute Toxicity Studies

	Species	#/sex	Route	Duration	Dose (g/kg)	Max. Safe Dose	Multiple of Max Human Dose	Primary Target organ(s) after Max. Safe Dose
1.	Rat	3	IV/SC	30 days	0.1, 0.3 0.9, 2.7 8.1	0.3	2.5	Hematopoietic (anemia), kidney & liver. At 8.1g/kg there was death; nephropathy.
2.	Dog	?	IV/SC	30-32 days	0.06, 0.18 0.54	0.54	4.5	No significant toxic changes.
3.	Dog (21-day old)	4	IV	35 days	0.1, 0.3 1.0	1.0	8.3	No significant toxic changes.
4.	Rat	30	IM	3 mos.	0.1, 0.3, 0.9*	0.3	2.5	Hematopoietic (mild anemia), kidney [*Toxicity at 0.9g/kg was considered to be of a minor nature.]
5.	Dog	3	IM	3 mos.	0.125, 0.25 0.5	0.5	4.2	No significant toxic changes.
6.	Dog	4	IV	6 mos.	0.085, 0.255 0.595, 0.850	0.85	7	No sig. toxic change. At the 3 highest doses, inc. acidophilic droplets in renal tubular epith. (dose-related) seen microscopically; electronmicroscopically believed to be heterolysosomes, but no ultrastructural damage was reported.
7.	Rat	10	SC	6 mos.	0.1, 0.5 2.5	0.5	?	High environmental temp. made meaningful conclusions difficult. F of HD died with acute & extensive hepatic necrosis; study invalidated by applicant & repeated (see #8).
8.	Rat	10	SC	6 mos	0.1, 0.3 0.9, 2.7	0.3	2.5	Liver, hematopoietic (anemia), kidney**

**Note: Kidney showed "functional change" microscopically at 0.9 & 2.7g/kg, i.e., inc. in the no. of eosinophilic droplets and brown granules in the cytoplasm of the proximal convoluted tubules, but no damage was encountered; changes thought to reflect urinary excretion of large quantities of proteins. Liver showed mild fibrosis around central veins & portal tracts at 2.7g/kg; only 2/10 rats were affected at 0.9g/kg.

Conclusions: The subacute toxicity studies in animals illustrated in Table 7 reveal that doses of 2.5x & 7x the human maximum dose in rats and dogs, respectively, are relatively well-tolerated. Potential target organs that could be affected adversely beyond these dose levels are the liver, kidney and the hematopoietic system. In these systems, the major findings were anemia, proximal tubular renal necrosis (see also nephrotoxicity studies) and mild fibrosis around the central veins and portal tracts. The anemia and kidney findings are common to this class of antibiotics. More recently, the liver has also been shown to be a target organ for structurally related compounds (pyridinium derivatives; e.g., cefsulodin, U-63,196E) to ceftazidime.

Recommendations

1. Animal toxicity studies indicate that the hematopoietic system, liver & kidney are targets for ceftazidime toxicity. If there have been related findings in humans, the MO may wish to put in the labeling some form of warning and/or recommendations for monitoring if the drug will be used for prolonged periods.

2. The labeling under "Usage in Pregnancy" should delete the word "rabbits"; this in view of the fact that maternally-related embryotoxicity was encountered at all doses (25-200mg/kg) used.

3. It is recommended that this drug be approved.

Samil C. Debbas, Ph.D.

cc: Orig. IND
HFN-140
HFN-140/MO
CSO
HFN-230
HFN-140/SCDebbas/smc/9/1/88
R/d init.by:JMDavitt
0034a

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

Form 5 50-570 (Amendment dated 4/5 84)

Date Review Completed: 6-15-84

Applicant: Glaxo, Inc

Drug: Fortaz® (ceftazidime for Inj. IM Injection)

Category: Cephalosporin antibiotic

Subject: Pyridine, 1% or less in the drug product after storage

Comments: This amendment was referred to me by Dr. King (HFN-315 Teratologist). In my review of this Form 5 (Original submission 5/2[illegible]; Pharm. Rev. dated 9/1/83) the issue of potential toxicity with pyridine levels of 1% or less present in ceftazidime was discussed (see pp. 25 & 26).

My earlier conclusion of accepting this limit for pyridine in ceftazidime has not changed to date. However, (see p. 26 of my review), NCI is conducting a carcinogenic study and EPA has recommended that mutagenicity & teratogenicity studies on pyridine be performed. Therefore, depending on the outcome of these studies, my position on this issue may change in the future.

Gamil C. Debbas

Gamil C. Debbas, Ph.D.

cc: Orig. IND
HFN-315
HFN-815/MO
CSO

HFN-220
HFN-815/GCDebbas/sne/6/18/84
R/d init.by:JMDavitt
0586b

BIO/DIS REV

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

TO

FROM

SUBJECT:

Ceftazidime is a [illegible] antibiotic for parenteral administration. It is administered at [illegible] IM or IV bolus dosing between 0.25 - 2.0 g every 8 to 12 hours depending on the susceptibility of the causative organism, the severity of infection and the condition and renal function of the patient.

The IV bolus injections of ceftazidime results in serum levels which decline with a biexponential decay, indicating a 2 compartment kinetic model. The kinetics of ceftazidime is linear between the dosage range of 0.5 and 2.0 g with a half-life of around 1.9 hour. The volume of central compartment is around 0.2L, plasma clearance around 115 ml/min, renal clearance around 100 ml/min. Approximately 80% of the administered drug is excreted unchanged by the kidneys in 24 hours. Probenecid has no effect on ceftazidime clearance (eliminating the possibility that the drug is eliminated probably by glomerular filtration. The system is fully or sufficiently effected by the renal function, it is advised [illegible] in patients with impaired renal function making it necessary to [illegible] in renal insufficiency. Protein binding for ceftazidime is less than 10%. The information provided in package insert reflect these findings.

Conclusion: The file supplement for [illegible] Form 3, Section is approvable.

[illegible]

Harry A. Skelly, Ph.D.
Acting Director
Division of Biopharmaceutics

Prepared by Vikram N. Dash, Ph.D.
RD initialed by Division Chief CDV

FT:dd:11/21/84

85 34069

MEMORANDUM

DATE: February 7, 1985

TO: Victoria Schauf, M.D., Medical Officer, HFN-815

FROM: G.C. Denbas, Ph.D., Pharmacologist, HFN-815

THRU: Supervisor, Pharmacologist, HFN-815

SUBJECT: Comparison of preclinical toxicity of [illegible] vs. ceftazidime [CFT (Form 5 50-5/82)] as per your request

For more detail than is discussed below, please see Forms 5 50-5"8 & pharmacology reviews dated 8/9/82* & 9/11/83*, respectively. The maximum dose to be given to humans for CFT & [illegible] are 6 g/day (120 mg/kg/day/50 kg adult) and 12 g/day (240 mg/kg/day), respectively.

The predicted margins of safety, as previously discussed* for both drugs, took into consideration the maximum clinical dose to be used and the dose found to be safe in preclinical subacute/subchronic studies conducted with these 2 drugs. The animal studies were run by each applicant under different sets of circumstances & experimental conditions; therefore, comparing the toxicity of both drugs is somewhat difficult and cannot be determined precisely unless both drugs are used in the same animal study under identical conditions. This undoubtedly is not the case here. Nevertheless, from our data base, using the subacute/subchronic studies of 3-6 mos. duration in rats, dogs & baboons, the following may be predicted based on the preclinical data.

1. Potential target organs that were adversely affected by both drugs are the liver, kidney & hematopoietic system. The anemia (species specific) & kidney findings are common to this class of antibiotics. The liver has also been shown to be a target organ for some other cephalosporins, e.g., U-63,196E.

2. The predicted margins of safety (see my two previous reviews) may be roughly summed up as follows:

	Species	Route	Duration	Max. Safe Dose (mg/kg)	Multiple of Max. Human Dose
CFT:	Rat	IM	3 mos.	300	2.5
		SC	6 mos.	300	2.5
	Dog	IM	3 mos.	500	4.2
		IV	6 mos.	850	7
	Rat	IM	3 mos.	100	0.416
		SC	6 mos.	60	0.25
	Dog	IM	3 mos.	100	0.416
		IM	6 mos.	100	0.416
	Baboon	?	3 mos.	150	0.625

While the margins of safety for the human dose are far from ideal for both drugs, it is apparent that has a relatively much lower margin of safety than CFT (i.e., it appears to be more toxic). However, it should be pointed out that these are long-term animal studies and the margins of safety may not apply rigorously if either drug is to be used for short periods of time (e.g., 7-10 days). My conclusions/recommendations to the MO, from the standpoint of pharmacology, are as follows:

1. Although the margins of safety are low for , this drug will be used for only one indication (pseudomonas aeruginosa), i.e. a high benefit category.

2. Use of this drug for clinically short periods of time should lessen the risk of any encountered toxicity, compared to its being used for long periods of time (1 month or more).

3. If this drug is clearly effective in short-term therapy (indications), I have no objection to its approval from the standpoint of pharmacology.

4. If this drug is clearly effective in long term therapy (indications), it could be approved for such periods with possibly clinical monitoring for liver & kidney function tests, especially if results of clinical studies on these organ systems indicate such a risk.

5. Whenever in 3 & 4 above, the drug is not clearly effective, it should not be approved for that clinical indication.

6. I will support your decisions, whatever they may be.

Gamil D. Debbas

Gamil C. Debbas, Ph.D.

cc: Form 5
50-578
HFN-815
HFN-815/GCDebbas/smc/2/11/85
R/d init.by:JHDavitt

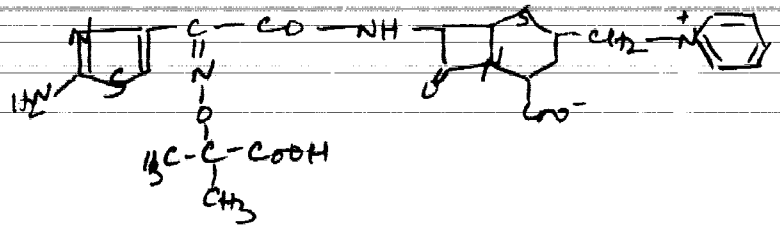
MAR 1 5 1984

Ceftazidime
Fortaz (for injection)
Form 5 #50-578
Reviewer: Vinod P. Shah, Ph.D.
Wang# 8202e

Glaxo Inc.
Research Triangle Park
North Carolina 27709
Submission Date:
May 20, 1983

Review of 15 Bioavailability Studies

Ceftazidime is a semi-synthetic broad-spectrum beta-lactam antibiotic belonging to the group of cepholosporins. It has the following structure:



Ceftazidime is administered parenterally (IV or IM). The sterile dry powder is a mixture of ceftazidime pentahydrate and sodium bicarbonate. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity. The pH of freshly reconstituted solutions usually range from 5.0 to 7.5.

Ceftizidime is administered as an I.V. infusion or IM injection at a dose ranging between 0.25-2.0 gm every 8 to 12 hours, depending on the susceptibility of the causative organisms, the severity of infection and the condition and renal function of the patient.

Bioavailability Studies:

All volunteers were healthy male members of Glaxo Staff, Glaxo Group Research Limited, Greenford, Middlesex, England, between the ages of 20 and 51 years. All studies were approved by an Ethical Review Committee (Institutional Review Board). An informed consent was received from all participating volunteers. The studies were monitored by the Medical Director, Dr. R.D. Foord and investigator Dr. Harding. The drug was administered either as IM, IV bolus or IV infusion.

All plasma and urine samples were analyzed by both HPLC method and Microbiological (MBA) method. The HPLC and MBA methods gave essentially same results, and therefore, the firm has used (tabulated) only MBA results in the submission. A correlation of 0.9805 was obtained between 491 pairs of serum data by two methods, and 0.9925 between 200 pairs of urine data. Protein binding was determined using Amicon ultrafiltration cone method and MBA analysis.

1. To study the Pharmacokinetics and Acceptability of ceftazidime - administered as a single IV dose of 250 mg (Study No. HVT/79/45 in Vol. 222).

   The study was carried out in 6 healthy male volunteers. Blood samples were collected at 5, 10, 15, 30, 45 min. and 1, 1.5, 2, 3, 4, 5 and 6 hours after injection. Urine samples were collected at 0-2, 2-4, 4-8 and 8-24 hours intervals. All samples were analyzed by microbiological method.

   The results of the study are given in Tables 1-4 and Figures 1 and 2. The serum level data best fitted a two compartment kinetic model using NONLIN. The elimination half-life was about 1.8 hours. No metabolites were detected in urine (HPLC method). The plasma clearance and renal clearance were 139 and 109 ml/min respectively.

2. To study the Pharmacokinetics and Acceptability of ceftazidime administered as a single IV dose of 500 mg; and to assess the effect of probenecid and to compare with cefotaxime, (Study No. HVT/79/47, Vol. 222).

   The study was carried out in 8 healthy male volunteers. The study design was as follows:

Subject No.	Week I	Week II
1, 2	ceftazidime	ceftazidime + Probenecid
3, 4	ceftazidime + Probenecid	ceftazidime
5 - 8	ceftazidime	cefotaxime

   Probenecid was administered as: 2 tablets (1 gm) at breakfast time, 1 tablet (500 mg) at 11 am and 1 tablet at 2.00 pm.

   Frequent blood samples up to 8 hours and urine samples up to 24 hours were collected and analyzed by MBA method. The results are summarized in Tables 5 - 12 and Figs. 3 - 4. The serum level data were fitted to two compartment model, and were comparable to the data obtained in study 1. Probenecid had no effect on the pharmacokinetic behavior of ceftazidime, indicating no renal tubular handling of this cepholosporin.

   The half-life of cefotaxime was 0.6 hours and plasma clearance was over 200 ml/min.

3. To study the Pharmacokinetics and Acceptability of ceftazidime administered as a single IV dose of 1 gm; and to assess the effect of probenicid and compare with cefotaxime (Study #HVT/79/48, Vol. No. 222).

The study design was similar to study 2. The results given in Tables 13-18 and Figures 5-6 substantiate the findings of the earlier study, indicating probenecid does not influence the pharmacokinetic behavior of ceftazidime. The AUC after 1 gm dose was approximately twice the AUC after 0.5 g dose, indicating dose proportionality.

4. To study the Pharmacokinetics of ceftazidime administered as IV infusion of 500 mg. (Study no. HVT/80/2-500 mg, Vol. 223).

The study was carried out in 6 healthy male volunteers. Ceftazidime in 20 ml was infused over 30 minute period. Blood samples were drawn at 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6 and 7 hours after the start of the infusion, and urine samples were collected over 24 hours period.

The results of the study are shown in Tables 19-22 and Figures 7-8. Serum concentrations at the end of the infusion were around 40 mcg/ml. The half-life of elimination was around 1.9 hours, Plasma clearance and renal clearance were 102 and 89 ml/min. About 87% of the drug was eliminated in 24 hours.

5. To study the Pharmacokinetics of ceftazidime administered as I.V. infusion of 1 g dose (Study No. HVT/80/2 - 1 g, Vol. 223).

This part of the study was carried out in 8 healthy male volunteers. The drug in 20 ml was infused over 20 minutes. Blood and urine samples were drawn as in the previous study. The results are shown in Tables 23 - 25 and Figures 9 - 10. Serum concentration at the end of infusion was around 69 mcg/ml and a total of 84% drug was recovered in urine in 24 hours. The mean AUC was 1.75 times the AUC from 500 mg infusion dose. All other parameters were same as before.

6. To study the pharmacokinetics of ceftazidime administered as an IV infusion of 2 g (Study No. HVT/80/7, Vol. No. 223).

The Study was carried out in 7 healthy male volunteers, and the drug was infused in 20 ml volume over 20 ml volume over 20 minutes period. Blood and urine samples were collected as before. The results are shown in Tables 26-29 and Figures 11 and 12. The serum concentration at the end of the infusion was 170 mcg/ml. The half-life was 1.9 hours, and 87% of the drug was recovered in urine in 24 hours. All other parameters were similar to 500 mg and 1 g dose, except AUC which was 266 mcg/ml, hour, 1.86 times AUC of 1 g dose.

These last three Studies indicate evidence of dose proportionality between 0.5 and 2 g dose.

7. To study the pharmacokinetics of ceftazidime when administered as a single IM dose of 500 mg.

The study was carried out in 8 healthy volunteers, and the dose was administered in 2 ml volume. Frequent blood and urine samples were collected and analyzed. Results are shown in Tables 30-33 and Figures 13-14.

The average Cmax was 17.6 mcg/ml, achieved in about 1 hour after IM injection. About 85% of the drug was recovered in 24 hours in urine. The data were fitted to one compartment model. Elimination half-life was around 2.2 hours. Plasma clearance was 106 ml/min and renal clearance was 90 ml/min. No metabolite was detected.

8. To study the absorption of ceftazidime after oral administration (Study No. HVT/80/11, Vol. 223).

The Study was carried out in 7 healthy male volunteers. A 250 mg dose was administered in aqueous sugar solution (20 ml) and urine sample was collected up to 12 hours and analyzed by HPLC and MBA method. No blood samples were collected. The results shown in table 34 indicate that the average urinary concentration was 1.5 mcg/ml and the average urinary recovery was less than 1% of the dose.

9. Multiple Dose Study. To investigate the tolerance of a 10 day course of 1 g tid IV and IM injections of ceftazidime, and to determine whether drug accumulation occurs or not with this dosing. (Study No. HVT/80/9, Vol. 223).

The study was carried out in 12 healthy male volunteers, 6 each for IV and IM study. The drug was administered IV in 10 ml volume over 10 - 20 min., and IM in 4 ml volume. After dose 1 and dose 25 IM, blood samples were drawn over 8 hours to define the blood level profile and to estimate pharmacokinetic parameters. Blood samples were taken immediately before and 20 minutes after IV infusion of dose 1, 2, 3, 19, 20, 21, 28, 29 and 30 to define the trough and peak serum levels. All samples were analyzed by MBA method.

The results of the study are shown in Table 35-38 and Figure 16. The average Cmax was 43.5 mcg/ml after dose 1 and dose 25 IM. The AUC after dose 1 was 174 mcg/ml x hour and after dose 25 was 186 mcg/ml x hour, indicating no accumulation of the drug. The half-life estimation was 2 hours and 2.2 hours after dose 1 and 25 respectively. There was no change in plasma clearance.

The average Cmax after first dose was 81.6 mcg/ml and the average trough value after the first dose was 7.5 mcg/ml. The average Cmax levels ranged from 90.5 to 107.3 mcg/ml thereafter with average trough values ranging from 0 to 9.3 mcg/ml. These results indicate that ceftazidime does not accumulate when administered as 1 g tid.

The IM dose of ceftazidime caused pain and discomfort. After 2 days,

the IM dose was administered in 1% lignocaine to lessen the discomfort of injection (except 25th dose, which was aqueous for the estimation of pharmacokinetic study).

10. Multiple dose study: To investigate tolerance of a 10 day course of 2 g tid IV administration of ceftazidime and to determine whether accumulation of drug or modification of the pharmacokinetic behaviour of the drug occurs or not as a result of such multiple dosing (Study No. HVT/80/26, Vol. 224).

    The Study was carried out in 8 normal healthy male volunteers. Samples were collected at 0, 10, 15, 30, 45 min. and 1, 1.5, 2, 3, 4, 6 and 8 hour after 1st dose and 28th dose for pharmacokinetic analysis.

    Blood samples were also taken just before dose 3, 4, 5, 6, and 8 to determine trough serum levels. Urine samples were collected for 0-2, 2-4 and 4-8 hour after doses 1 and 28.

    The results of the Study are summarized in Tables 39-46 and Figure 17, and indicate no drug accumulation when administered 2 g tid for 10 days. The blood level profile after 1st and 28th dose were similar. The trough values were around 5.3 to 8.6 mcg/ml. Urinary recoveries averaged 81.2% after dose 1 over the first 8 hour and 76.3% after dose 28. The average elimination half-life was 1.8 hour.

11. Pharmacokinetics of ceftazidime in special population: (Vol. 225).

    a) In neonates, infants and children:

    This is a review of multi-center study involving neonates, infants and children. The serum levels of ceftazidime in infants 2 months to one year of age given single 30 mg/kg dose matched those found in adults given 2 g (30 mg/kg for 70 kg adult) IV dose (Table 47). On the other hand levels in infants were higher. The average elimination half-life in infants-children was 1.8 hours, similar to adults, where as the half-life in neonates was around 4.2 hours.

    The half-life in children with cystic fibrosis was shorter (1.3 hours) then in those without (1.8 hours) Cystic fibrosis.

    b) Pharmacokinetics of ceftazidime in elderly (Ref: J. Antimierolil Chemotherapy, 1962, 10, 199-206).

    The data from two trials involving elderly patients have been gathered. Patients over 70 years age with stable renal function and with infections not involving renal tract were studied. Renal function was assayed by ^{51}CR-EDTA clearance. The

results are summarized in Table 48. No correlation was observed between age and ceftazidime half-life. However, a good correlation (Fig. 18) was observed between EDTA clearance and serum elimination rate constant, indicating renal function, often reduced in the elderly, is of paramount importance in influencing the rate of elimination.

2. Pharmacokinetics of ceftazidime in Pediatrics: Single and Multiple dose studies (Study No. K02 and K13, Vol. 226).

The Study in pediatric population was conducted by Dr. J.D. Nelson, University of Texas, Health Science Center at Dallas, South Western Medical School, Dallas, Texas and was monitored by Dr. J.M. Chubb of Glaxo.

A total of 33 children participated in single dose study.

Age	M	F	Total
1-6m	4	2	6
7-11m	2	3	5
1-2y	2	7	9
3-6y	1	2	3
7-12y	5	5	10
Total	14	19	33

A dose of 15, 25, 30 or 50 mg/kg of ceftazidime was administered IV. Blood samples were taken at 0, 15, 30 45, 60 min., 2, 4 and 6 hrs. and analyzed microbiologically. A summary of these data is shown below.

Dose mg/kg	M	Cmax-mcg/ml Mean ± SEM		AUC Mcg/ml•hr Mean ± SEM		Half-life hr Mean ± SEM	
15	8	37.6	4	65.7	11	1.6	0.2
25	1	78.0	---	121.4	---	1.8	---
30	5	66.0	4	120.2	9	1.7	0.2
50	6	178.0	23	294.8	52	1.9	0.4

Age	n	Half-life - hr Mean ± SEM		Vd (L/Kg) Mean ± SEM	
1-2 m	10	2.0	0.2	0.55	0.04
14-24 m	4	1.5	0.3	0.83	0.18
> 2 y	6	1.5	0.2	0.49	0.06

The results of the study indicate that the kinetics of ceftazidime were linear in children in dose range of 15-50 mg/kg. Children under 1 year of age showed a slightly higher elimination half-life than older children.

These results substantiate the findings of other investigators and suggest that a dose of 25 to 50 mg/kg up to a maximum dose of 2 gm 8 hourly can be administered to children 1 month of age and older (with normal renal function).

A total of 10 patients participated in multiple dose study.

Age	M	F	Total
1-6 mo	1	2	3
1-2 y	1	1	2
3-6 y	-	2	2
7-12 y	1	2	3
Total	3	7	10

Ceftazidime was administered as IV infusion over 15 minutes every 8 hours at an approximate dose of 50 mg/kg to 5 non-cystic patients and at a dose of 75 mg/kg to 5 cystic patients for 2-3 days. Blood samples were collected at 0, 0.5, 1, 2, 4 and 6 hours after the infusion of 3rd or 4th dose and the last dose of ceftazidime. Unfortunately, collection of serum samples beyond 6 hour post administration were not obtained, and consequently the calculations dervived from this data reflects approximately true pharmacokinetic parameters. However, the data are useful in providing necessary information concerning the dosage regimen. The results of the study shown in Table 49 indicate the half-life to be 1.3 hr in non-cystic patients and 1.1 hr in cystic patients.

Accumulation of ceftazidime does not occur at the doses used. Minor differences observed between cystic fibrosis and non-cystic fibrosis children do not appear to be of clinical significance. The results from this trial suggest that a dosage regimen of 50 mg/kg 8 hourly would be clinically effective in the treatment of infections caused by susceptible pathogens in children 1 month of age and greater. A larger dose of 75 mg/kg administered 8 hourly may be indicated in children with cystic fibrosis.

13. Pharmacokinetics of ceftazidime in neonates: (Study K17, Vol. 226).

The study was carried out by Dr. M. Gooch of Primary Children's Hospital, Salt Lake City, Utah and monitored by Dr. Chubb of Glaxo.

The study was designed to assess the pharmacokinetics of ceftazidime in neonates between 1 and 9 days of age. Single 30 mg/kg dose of ceftazidime was administered as IV infusion over 30 min. and blood samples were collected at 0, 15, 30 and 60 minutes, 2, 4, and 8 hours after infusion and analyzed by Dr. Meyer of University of Tennessee.

The following patients participated in the study:

Age-Days	M	F	Total
1	1	-	1
2	2	2	4
3	-	2	2
5	1	1	2
7	-	1	1
9	1	-	1
Total	5	6	11

The results from 10 of 11 patients shown in Table 50 indicate that elimination half-life ranged between 2.8 to 6.9 hours (mean 4.7 hrs). The mean total body clearance was 0.1 L/hr/kg. The serum concentrations in neonates from dose of 30 mg/kg were comparable to the concentrations found in adults following a 1.0 g dose. The elimination half-life was significantly prolonged due to immature renal excretion mechanism in neonates (1-9 days). The results indicate that a dose of 30 mg/kg bid can be administered to neonates (1-9 days) for achieving therapeutic concentrations.

14. The pharmacokinetics of ceftazidime in patients with impairment of renal function. (Vol. 225).

Four studies have been published describing serum levels and elimination half-lives from patients with varying degrees of impairment of renal function. The studies included 23 healthy volunteers and 67 patients.

Gower P E, Hobbs P M and Harding S M, Kinetics of ceftazidime in renal impairment, Current Chemotherapy and Immunology, Proceedings of the 12th International Congress of Chemotherapy (1982), 1, 498-499

Norrby S R, Burman L A, Linderholm H and Trollfors B, Ceftazidime: pharmacokinetics in patients and effects on the renal function, Journal of Antimicrobial Chemotherapy (1982), 10, 199-206

Hoeffler D, Koeppe P and Williams K J, The pharmacokinetics of ceftazidime in normal and impaired renal function (A report)

Olier B, Leguy F, Borsa F, Spencer G R, Fillastre J P and Humbert G, Pharmacokinetics of ceftazidime in uraemic patients, Abstracts of the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Oct 1982, Miami, USA), Abstract 806, and correspondence

Straughn A B, Meyer M C, Acchiardo S, Chubb J and Comstock T J, Pharmacokinetics of ceftazidime in normal subjects and end stage renal disease patients on haemodialysis, Abstracts of the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Oct 1982, Miami, USA), Abstract 801

In the study of Gower et. al., 14 patients with impaired renal function were administered a single dose of 1 g ceftazidime. Frequent serum and urine samples were collected and analyzed by HPLC method. The GFR was estimated in the patients by using ^{51}Cr-EDTA clearance. The relationship between ceftazidime serum half-life and GFR is shown in Fig. 19, the half-life increased when GFR was reduced. The half-life was 1.9 hours at an average GFR of 115 ml/min in healthy volunters compared to 16.7 hr at an average GFR of 12 ml/min in patients. There was no change in Vd. Similar observation was made by Hoeffler et. al and Olier et. al. The results are summarized in Table 51 to 56 and Figure 20. Using the regression line from Fig. 20, a relationship between GFR and predicted steady state trough levels were obtained, and is shown in Fig. 21. The results indicate that a dose reduction as well as interval adjustment is necessary with impaired renal function (lower GFR).

The normal daily dose for adults is 3 to 4 g given as either 1 g 8 hourly or 2 g 12 hourly. In patients with impaired renal function, an initial loading dose may be given, followed by the following maintenance dose:

Recommended maintenance doses of ceftazidime in renal insufficiency

Creatinine clearance (ml/min)	Approx serum creatinine* (μmol/l)	Recommended unit dose of ceftazidime (g)	Frequency of dosing (h)
50-31	150-200	1.0	12
30-16	200-350	1.0	24
15-6	350-500	0.5	24
< 5	500	0.5	48

* These values are merely guide-lines and may not accurately predict renal function in all patients and especially in the elderly in whom the serum creatinine may overestimate renal function.

15. A single dose pharmacokinetic study of ceftazidime in patients with normal and impaired renal function (Study No. K04, Vol. 226).

This was a multi-center study monitored by Dr. J.M. Chubb of Clinical Research Division, Glaxo, Research Triangle Park, North Carolina. The study was carried out by (1) Dr. W. L. George, V.A. Wadsworth Medical Center, Los Angeles, CA and (2) Dr. S.R. Acchiardo, University of Tennessee, Memphis Tennessee.

Based upon the creatinime clearance, the subjects were divided into the following groups:

Group	Creatinine clearance
I	> 60 ml/min
II	30-60 ml/min
III	15-30 ml/min
IV	< 15 ml/min
V	Dialysis patients

A single one gm. IV dose of ceftazidime was administered over 2-3 minutes. Blood samples were collected at 0, 5, 15, 30, 60, 90 min and 2, 4, 6, 8, and 12 hour after injection. Additional blood samples at 18, 24 and 36 hours were collected from volunteers in III, IV and V groups. Urine samples at 0-2, 2-4, 4-8, and 8-12 hour intervals after the drug administration were also collected. Additonal urine samples for the period 12-16, 16-24 and 24-36 hours were collected from volunteers in II and IV groups. All samples were analyzed by HPLC method. The results from both the center studies were similar and are shown in Table 57 and Figure 22-23. The results of the study demonstrate that as renal function decreases, the length of time necessary to eliminate a dose of ceftazidime increases. The average half-life in healthy adults (normal renal function) was around 2 hours. Whereas in patients with creatinine clearance of 15 ml/min, the half-life was around 15.4 hours. The volume of distribution was unrelated to renal function.

From this single dose data, predictions of maximum and minimum serum concentrations were made for different dosage regimens in the presence of varying levels of renal function based upon following equations.

$$CSS\ MAX = \frac{(D/INFT)\ (1-e^{-\beta INFT})}{\beta \times VDSS\ (1-e^{-\beta T})}$$

$$CSS\ MIN = CSS\ MAX\ e^{-\beta(T - INFT)}$$

where:

CSS MAX = Steady state maximum concentrations
D = Total dose infused
INFT = Infusion time
β = Overall elimination rate constant from two compartment model.
VDSS = Volume of distribution steady state
τ = Dosing interval
CSS MIN = Steady state minimum concentration

The results of these predictions are shown in Table 58.

In individuals with creatinine clearances greater than 50 ml/min/1.73M^2, a dose of 1.0G 8 hourly would be adequate to provide serum concentrations within the range between 20 and 80 mcg/ml over an 8 hour dosing interval. In individuals with creatinine clearances below 50 ml/min, the interval between doses must be lengthened, and at very low levels of renal function, the dose must also be reduced to maintain serum concentrations between 20 and 80 mcg/ml. The following recommendations is made as a dosing guideline based upon the predictions in Table 58.

Creatinine Clearance (ml/min)	Dosage
> 50	Normal dose and schedule
31 - 50	1000mg every 12 hours
16 - 30	1000mg every 24 hours
6 - 15	500mg every 24 hours
< 6	500mg every 48 hours

Overall Summary:

The IV bolus injections of ceftazidime results in serum levels which declined with a biexponential decay, indicating a 2-compartment kinetic model. Average values for various kinetic parameters were:

Parameter	Rate: h^{-1}	half-life (hr)
α	5.8	0.2
β	0.4	1.8
k 12	2.73	0.4
k 21	2.54	0.3
kel	0.89	0.8

Volume of central compartment = 8.9L
Volume of peripheral compartment = 8.6L

0-2 hr urinary excretion = 51%
0-24 hr urinary excretion = 83%
Plasma clearance: 115 ml/min
Renal clearance: 106 ml/min
Creatinine clearance: 116
Ceftazidime/creatinine clearance ratio = 0.91

The kinetics of ceftazidime were linear between the dose range of 0.5 and 2.0 gm, with a half-life of around 1.9 hours after I.V. administrations. The mean Cmax after 0.5, 1.0 and 2.0 g I.V. infusion over 20-30 minutes was 42, 69 and 170 mcg/ml respectively. The mean Cmax after 0.5 and 1.0 g IM injection was 17 and 39 mcg/ml respectively at approximately 1 hour. The half-life was around 2 hours. Approximately 80% of the drug administered is excreted unchanged by the kidneys in 24 hours. The mean renal clearance of ceftazidime is 100 ml/min. Probenecid has no effect on ceftazidime clearance (eliminatin) indicating that the drug is eliminated completely by glomerular filtration only. The serum half-life is significantly effected by the renal function, and is prolonged in patients with impared renal function. Consequently, the dosage adjustment is needed in patients with impaired renal function.

Protein binding for ceftazidime was less than 10%.

Conclusion: Application Acceptable

The bioavailability-pharmacokinetic studies described by the firm in their submission (Volumes 222-226, dated May 20, 1983) on ceftazidime are found to be acceptable by the Division of Biopharmaceutics. The Division of Biopharmaceutics has determined that the firm has fulfilled all the necessary elements of bioavailability/ bioequivalence requirements.

The above recommendation should be forwarded to the firm.

V. P. Shah 12/24/83

Vinod P. Shah, Ph.D.
Pharmacokinetics Branch

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11/20/83:mstephens:(8202e):FT:kk:12/19/83

cc: Form 5: 50-578, HFN-140, HFN-525 (Shah), Review, Drug, Division and Chron File.

Table I - HVT/79/45

Serum levels of ceftazidime by MBA after an intravenous bolus injection of 250mg ceftazidime to 6 male volunteers

Volunteer Number	Ceftazidime concentration (mg/l) at time after dose:											
	5 min	10 min	15 min	30 min	45 min	1 h	1½ h	2 h	3 h	4 h	5 h	6 h
1	22.0	17.4	15.7	13.4	9.2	7.2	6.5	4.3	2.8	1.6	≈1.0	1.5
2*	18.4*	13.8*	12.3*	9.9	9.0	7.1	4.7	4.2	3.3	1.8	1.9	1.6
3	21.0	23.0	11.1	10.6	8.5	7.5	5.3	4.6	3.3	1.9	1.7	≤1.0
4†	18.0	18.1	15.0	11.9	8.6	8.0	6.1	4.9	3.1	2.2	1.9†	1.4
5	18.5	13.7	10.0	10.0	8.2	8.2	6.0	4.5	2.4	1.9	1.5	≤1.0
6	19.6	15.0	10.6	10.1	8.0	7.6	6.0	5.9	2.8	2.7	2.2	1.8
Average	19.8	17.4	12.5	11.0	8.6	7.6	5.8	4.7	3.0	2.0	1.8	1.6
Standard deviation	1.7	3.6	2.7	1.4	0.4	1.5	0.7	0.7	0.3	0.4	0.3	0.1

* V2 : 5 min sample at 6 min
10 min sample at 12 min
15 min sample at 18 min

† V4 : 5 h sample at 5 h 40 min

Table II - HVT/79/45

Percentage urinary recoveries of ceftazidime by MBA after an intravenous bolus injection of 250mg ceftazidime to 6 male volunteers

Volunteer Number	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1	50.6	15.0	13.3	4.3	83.2
2	48.8	18.5	9.5	3.7	80.5
3	47.5	19.7	10.9	2.9	81.0
4	20.6	8.8	16.1	14.5	60.0
5	52.1	16.2	9.6	2.4	80.3
6	41.0	24.4	10.7	3.3	79.4
Average	43.4	17.1	11.7	5.2	77.4
Standard deviation	11.8	5.1	2.5	4.6	8.9
Cumulative average	43.4	60.5	72.2	77.4	

Table IV - HVT/79/45

Computer derived pharmacokinetic parameters of ceftazidime from MBA data after an intravenous bolus injection of 250mg ceftazidime to 6 male volunteers

Volunteer Number	Initial concentration (mg/l)	Apparent volume of distribution (l)	Volume of central compartment (l)	Volume of peripheral compartment (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	24.9	15.8	10.0	5.8	28.9	144	122	1.4
2	29.4	18.6	8.5	10.1	27.5	152	122	1.5
3	28.7	18.7	8.7	10.0	30.2	138	112	1.8
4	20.7	21.4	12.0	9.4	34.2	122	73	2.5
5	36.8	18.6	6.8	11.8	27.3	152	123	1.5
6	31.7	20.4	7.9	12.5	32.8	127	101	2.0
Average	28.7	18.9	9.0	9.9	30.2	139	109	1.8
Standard deviation	5.6	1.9	1.8	2.3	2.8	13	20	0.4

(1)
Table 4

Table V - HVT/79/45

Clearance values for creatinine and ceftazidime after a bolus intravenous injection of 250mg ceftazidime to 6 male volunteers

Volunteer Number	Creatinine Clearance (ml/min)	Renal Clearance Ceftazidime (ml/min)	Renal Clearance Ratio Ceftazidime/ Creatinine
1	109	122	1.12
2	116	122	1.05
3	126	112	0.89
4	122	73	0.60
5	145	123	0.85
6	134	101	0.75
Average	125	109	0.88
Standard deviation	13	20	0.19

Table I - HVT/79/47

Serum levels of ceftazidime by MBA after an intravenous bolus injection of 500mg ceftazidime to 8 male volunteers

Volunteer Number	(Part)	ceftazidime concentration (mg/l) at time after dose: 5 min	10 min	15 min	30 min	1 h	1½ h	2 h	3 h	4 h	6 h	8 h
1	(I)	49.0	34.5	33.0	24.2	17.0	14.1	10.3	7.3	4.8	2.8	2.1
2	(I)	48.0	41.0	35.5	27.3	19.2	14.9	12.9	7.3	5.5	2.7	1.8
3	(II)	33.0	35.5	27.8	15.2	9.1	11.0	9.5	8.9	6.9	2.1	1.1
4	(II)	39.5	31.0	34.0	17.0	14.1	10.7	9.0	7.2	7.1	2.5	0.6
5	(I)	58.0	52.0	40.0	34.5	20.2	16.1	11.7	7.0	4.5	2.1	0.6
6	(I)	42.0	36.0	33.5	27.0	21.0	15.6	13.1	8.9	7.0	3.0	2.3
7	(I)	50.0	42.0	34.0	26.2	18.0	12.2	11.8	7.2	4.8	2.5	0.9
8*	(I)	51.0	41.5	35.0	24.8	18.1	15.1	9.3*	6.8	4.1	1.9	0.9
Average		46.3	39.2	34.1	24.5	17.1	13.7	11.2	7.6	5.6	2.4	1.3
Standard deviation		7.8	6.5	3.3	6.1	3.8	2.1	1.6	0.9	1.3	0.4	0.6

* V8 : 2 h sample at 2½ h

Table II - HVT/79/47

Serum levels of ceftazidime by MBA after an intravenous bolus injection of 500mg ceftazidime to 4 male volunteers also taking probenecid

Volunteer Number (Part)	Ceftazidime concentration (mg/l) at time after dose: 5 min	10 min	15 min	30 min	1 h	1½ h	2 h	3 h	4 h	6 h	8 h
1 (II)	50.0	33.0	28.5	24.9	19.8	14.3	9.9	9.5	6.8	3.6	1.8
2 (II)	39.5	30.5	32.5	28.7	19.8	15.0	11.1	11.1	6.4	3.1	0.9
3 (I)	47.0	35.5	35.5	29.0	18.6	15.3	11.7	7.0	4.7	2.4	1.8
4* (I)	45.5*	40.0	35.5	26.2	17.3	13.2	10.6	6.3	4.6	2.1	0.7
Average	45.5	34.8	33.0	27.2	17.6	14.4	10.8	8.5	5.6	2.8	1.3
Standard deviation	4.4	4.0	3.3	2.0	2.2	0.9	0.8	2.2	1.2	0.7	0.6
Without probenecid V1 - V4 (Table I)											
Average	42.4	35.5	32.6	20.9	14.8	12.7	10.4	7.7	6.1	2.5	1.4
Standard deviation	7.6	4.2	3.3	5.8	4.4	2.1	1.7	0.8	1.2	0.3	0.7

* V4 : 5 min sample at 6 min

Table III - HVT/79/47

Serum levels of cefotaxime by HBA after an intravenous bolus injection of 500mg cefotaxime to 4 male volunteers; comparison with ceftazidime

Volunteer Number (Part)	Cefotaxime concentration (mg/l) at time after dose: 5 min	10 min	15 min	30 min	1 h	1½ h	2 h	3 h	4 h	6 h	8 h
5 (II)	51.0	36.0	30.5	16.0	8.5	3.7	2.5	1.0	1.0	0	0
6 (II)	48.0	35.0	26.0	20.0	9.1	5.0	3.1	1.5	1.0	1.2	0
7* (II)	45.0*	35.0	28.5	16.5	7.1	4.8	2.9	1.8	1.0	0	0
8 (II)	49.0	38.0	33.0	20.0	10.5	6.4	3.4	1.8	1.0	0	0
Average	49.3	36.0	29.5	18.1	8.8	4.5	3.0	1.5	1.0	0.3	0
Standard deviation	1.5	1.4	3.0	2.2	1.4	0.7	0.3	0.1		0.6	
ceftazidime (Part I) V5 - V8 (Table I)											
Average	50.2	42.9	35.6	28.1	19.3	14.8	12.2	7.5	5.1	2.4	1.2
Standard deviation	6.6	6.7	3.0	4.4	1.5	1.7	0.7	0.9	1.3	0.5	0.8

* V7 : 5 min sample at 2½ min

V8 : 1½ h sample 2 min late

Table V - HVT/79/47

Percentage urinary recoveries of ceftazidime by MBA after an intravenous bolus injection of 500mg ceftazidime to 8 male volunteers

Volunteer Number (Part)	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1 (I)	49.9	16.6	11.8	1.8	80.1
2 (I)	48.2	18.0	10.9	4.2	81.3
3 (II)	43.7	17.6	11.3	5.3	77.9
4 (II)	51.3	20.9	11.4	4.0	87.6
5 (I)	55.8	15.6	6.6	3.1	81.1
6 (I)	49.1	17.0	11.9	6.1	84.1
7 (I)	62.0	14.6	8.6	3.5	88.7
8 (I)	76.0	16.6	8.6	2.5	103.7
Average	54.5	17.1	10.1	3.8	85.6
Standard deviation	10.3	1.9	1.9	1.4	8.2
Cumulative average	54.5	71.6	81.7	85.5	

(2)
Tab. 9

Table VI - HVT/79/47

Percentage urinary recoveries of ceftazidime by MBA after an intravenous bolus injection of 500mg ceftazidime to 4 male volunteers also taking probenecid

Volunteer Number (Part)	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1 (II)	47.0	23.4	11.7	6.9	89.0
2 (II)	48.0	20.6	15.4	3.8	87.8
3 (I)	41.0	22.9	20.4	3.9	88.2
4 (I)	57.8	15.7	10.3	3.3	87.1
Average	48.4	20.6	14.4	4.5	88.0
Standard deviation	6.9	3.5	4.5	1.6	0.8
Cumulative average	48.4	69.0	83.4	87.9	
Without probenecid V1 - V4 (Table V)					
Average	48.3	18.3	11.3	3.8	81.7
Standard deviation	3.3	1.8	0.5	1.5	4.2
Cumulative average	48.3	66.6	77.9	81.7	

Table XI - HVT/79/47

Computer derived pharmacokinetic parameters of ceftazidime from MBA data after an intravenous bolus injection of 500mg ceftazidime to 8 male volunteers

Volunteer Number	(Part)	Initial concentration (mg/l)	Apparent volume of distribution (l)	Volume of central compartment (l)	Volume of peripheral compartment (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	(I)	70.2	14.8	7.1	7.7	66.3	126	101	1.5
2	(I)	57.0	14.7	8.8	5.9	75.4	110	89	1.7
3*	(II)	43.1	26.1	11.6	14.5	72.0	116	90	2.9
4*	(II)	47.1	23.5	10.6	12.9	66.7	125	109	2.5
5	(I)	68.8	11.3	7.3	4.0	74.7	112	91	1.3
6	(I)	47.2	15.6	10.6	5.0	81.7	102	86	1.9
7	(I)	61.7	15.1	8.1	7.0	69.3	120	106	1.6
8	(I)	65.9	14.3	7.6	6.7	68.9	121	125	1.5
Average		57.6	16.9	9.0	8.0	71.9	116	100	1.9
Standard deviation		10.7	5.1	1.7	3.8	5.2	8	11	0.6

* V3 : analysed omitting 1 h value
V4 : analysed omitting 4 h value

Table XII — HVT/79/47

Computer derived pharmacokinetic parameters of ceftazidime from MBA data after an intravenous bolus injection of 500mg ceftazidime to 4 male volunteers also taking probenecid

Volunteer Number (Part)	Initial concentration (mg/l)	Apparent volume of distribution (l)	Volume of central compartment (l)	Volume of peripheral compartment (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1 (II)	88.9	16.2	5.6	10.6	73.0	114	102	1.8
2 (II)	40.0	17.1	12.5	4.6	81.6	102	90	2.1
3* (I)	53.6	14.2	9.3	4.9	72.0	116	102	1.6
4 (I)	54.4	15.2	9.2	6.0	66.4	126	109	1.6
Average	59.2	15.7	9.2	6.5	73.2	114	101	1.8
Standard deviation	20.9	1.3	2.8	2.8	6.2	10	8	0.2
Without probenecid V1 - V4 (Table XI)								
Average	54.4	19.8	9.5	10.2	70.1	119	98	2.2
Standard deviation	12.1	5.9	2.0	4.1	4.4	8	9	0.7

* V3 : analysed omitting 10 min serum value

Table XVI HVT/79/47

Clearance values for creatinine and ceftazidime after an intravenous bolus injection of 500mg ceftazidime to 8 male volunteers: effect of probenecid. 4 volunteers

Without probenecid

volunteer number (Part)	Creatinine clearance (ml/min)	Renal clearance (ml/min)	Drug/creatinine clearance ratio
1 (I)	164	101	*
2 (I)	193	89	*
3 (II)	112	90	0.80
4 (II)	104	109	1.05
5 (I)	129	91	*
6 (I)	129	86	*
7 (I)	191	106	*
8 (I)	211	125	*
Average standard deviation	154 41	100 13	*
V1-V4 Average standard deviation	143 43	98 9	*

With probenecid

1 (II)	90	102	1.13
2 (II)	143	90	0.63
3 (I)	219	102	*
4 (I)	201	109	*
Average standard deviation	163 59	101 8	*

* value for creatinine clearance suspect i.e. values for part I)

Serum levels of ceftazidime [illegible]
1g ceftazidime to 8 male volunteers

Volunteer Number	(Part)	Ceftazidime concentration (mg/l) at time after dose: 5 min	10 min	15 min	30 min	1 h	1.5h	2 h	3 h	4 h	6 h	8 h
1	(II)	84.0	68.0	61.5	44.0	31.5	27.0	23.8	13.5	8.6	4.3	2.7
2	(II)	82.0	66.0	55.0	35.8	34.5	29.0	26.0	15.9	10.2	6.2	3.2
3	(II)	85.0	64.0	52.0	30.0	23.3	18.0	13.5	8.5	5.1	2.7	1.5
4	(II)	100.0	81.0	58.0	56.0	43.0*	31.5	31.0	16.5	15.0	7.2	4.7
5	(II)	NS	78.0	61.0	43.0	24.5	22.0	17.8	12.0	7.0	4.2	2.9
6	(II)	75.0	77.5	64.0	52.0	38.5	31.5	23.0	16.0	12.7	6.6	4.5
7	(I)	110.0	74.0	69.0	48.5	29.2	26.2	18.5**	10.3	9.4	4.7	2.3
8	(I)	76.0	76.0	59.0	39.0+	37.0+	30.5+	27.0	11.8	9.7	6.4	3.7
Average		87.4	73.1	59.9	45.3	32.1	26.5	23.2	13.1	9.7	5.3	3.2
Standard deviation		13.0	6.3	5.2	7.3	7.1	5.0	5.8	2.9	3.1	1.5	1.1

NS = No Sample

* V6 : 1 h sample at 1 h 1 min

** V7 : 2 h sample at 2 h 9 min

\+ V8 : 30 min sample at 31 min
1 h sample at 1 h 8 min
1.5 h sample at 1 h 35 min

Table V - HVT/79/48

Percentage urinary recoveries of ceftazidime by MEA after an intravenous bolus injection of 1g ceftazidime to 8 male volunteers

Volunteer Number (Part)	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1 (II)	54.1	17.4	12.8	3.7.	88.0
2 (II)	58.6	14.6	12.3	4.8	90.3
3 (II)	61.1	17.3	8.6	2.8	89.8
4 (II)	50.4	20.0	11.9	5.1	87.4
5 (II)	53.4	14.7	10.8	3.6	82.5
6 (II)	51.9	16.1	12.6	4.9	85.5
7 (I)	50.4	20.4	8.1	2.8	81.7
8 (I)	43.6	16.2	11.7	4.4	75.9
Average	52.9	17.1	11.1	4.0	85.1
Standard deviation	5.3	2.1	1.8	1.0	4.9
Cumulative average	52.9	70.0	81.1	85.1	

Table XII - HVT/79/48

Computer derived pharmacokinetic parameters of ceftazidime from MBA data after an intravenous bolus injection of 1g ceftazidime to 4 male volunteers also taking probenecid

Volunteer Number (Part)	Initial concentration (mg/l)	Apparent volume of distribution (l)	Volume of central compartment (l)	Volume of peripheral compartment (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
5 (I)	81.1	20.8	12.3	8.5	139.3	120	106	2.3
6 (I)	96.7	19.7	10.3	9.4	161.6	103	102	2.5
7 (II)	139.7	12.4	7.2	5.2	190.5	119	104	1.3
8 (II)	94.7	16.0	10.6	5.4	133.4	125	99	1.6
Average	103.0	17.2	10.1	7.1	143.7	117	103	1.9
Standard deviation	25.4	3.8	2.1	2.2	12.4	9	3	0.6
Without probenecid V5 - V8 (Table XI)								
Average	116.6	17.0	9.1	7.9	136.7	124	101	1.8
Standard deviation	35.0	2.2	2.5	2.1	20.9	18	16	0.5

Table I - HVT/80/2 - Part 1

Serum levels of ceftazidime by MBA after an intravenous infusion of 500mg ceftazidime over 30 min to 6 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) at time after dose:										
	10 min	20 min	30 min	45 min	1 h	1½ h	2 h	3 h	4 h	6 h	7 h
1	15.0	26.0	52.0	31.0	25.5	17.0	12.5	8.8	6.9	3.3	2.9
2	25.0	29.0	39.0	25.0	22.5	15.5	12.5	8.9	6.1	3.1	1.9
3	18.8	32.0	42.0	28.0	25.0	17.5	12.5	10.5	5.9	3.6	2.7
4	17.5	31.5	44.0	32.0	25.0	17.2	14.0	10.0	7.5	4.1	3.1
5	19.0	34.0	38.0	32.0	25.0	15.5	10.0	7.9	3.8	1.8	1.3
6	21.0	31.0	34.0	29.0	24.5	17.5	12 5	9.2	5.8	3.1	2.4
Average	19.4	30.6	41.5	29.5	24.6	16.7	12.3	9.2	6.0	3.2	2.4
Standard deviation	3.4	2 ?	6.1	2.7	1.1	1.0	1.3	0.9	1.3	0.8	0.7

223 017

Table II - HVT/80/2 - Part I

Percentage urinary recoveries of ceftazidime by MBA after an intravenous infusion of 500mg ceftazidimeover 30 min to 6 male volunteers

Volunteer Number	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1	29.9	42.6	13.1	1.6	87.2
2	53.1	21.6	12.9	3.8	91.4
3	58.4	22.8	12.4	5.3	98.9
4	36.2	17.1	12.7	1.6	67.6
5	63.0	20.0	7.0	1.6	91.6
6	41.5	24.1	14.0	4.8	84.4
Average	47.0	24.7	12.0	3.1	86.8
Standard deviation	13.1	9.1	2.5	1.8	10.6
Cumulative average	47.0	71.7	83.7	86.8	

Table IV - BVT/80/2 - Part I

Pharmacokinetic parameters of ceftazidime from MBA data after an intravenous infusion of 500mg ceftazidime over 30 min to 6 male volunteers

Volunteer Number	Peak concentration (mg/l)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	52.0	16.6	87	96	84	2.0
2	39.0	16.7	78	108	98	1.8
3	42.0	16.4	86	97	96	2.0
4	44.0	16.4	92	90	61	2.1
5	38.0	15.2	69	120	110	1.5
6	34.0	16.5	81	103	87	1.8
Average	41.5	16.3	82	102	89	1.9
Standard deviation	6.2	0.6	8	11	18	0.2

Tab 4

Table V - HVT/80/2 - Part I

Clearance values for creatinine and ceftazidime after an intravenous infusion of 500mg ceftazidime over 30 min to 6 male volunteers

MBA data

Volunteer Number	Creatinine Clearance (ml/min)	Renal Clearance ceftazidime (ml/min)	Renal Clearance Ratio ceftazidime/Creatinine
1	97	84	0.87
2	128	98	0.77
3	116	96	0.83
4	106	61	0.58
5	140	110	0.79
6	128	87	0.68
Average	119	89	0.75
Standard deviation	16	18	0.11

Table I - HVT/80/2 - Part II

Serum levels of ceftazidime by MBA after an intravenous infusion of 1g ceftazidime over 20 min to 7 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) at time after dose:										
	10 min	20 min	30 min	45 min	1 h	1.5h	2 h	3 h	4 h	6 h	8 h
1*	48.0*	74.0	60.0	54.0	40.0	31.0	25.5	11.5	11.0	4.7	2.8
2*	55.0*	74.0	66.0	53.0	36.5	35.0	23.5	13.8	11.2	5.5	3.2
3	44.0	75.0	60.0	47.0	39.5	29.0	21.0	14.0	9.6	5.4	3.0
4*	36.0*	38.5	61,0	48.0	41.0	28.5	27.0	15.5	13.0	7.9	4.4
5*	52.0	64.0	60.0	48.0*	34.0	28.0	19.2	12.0	8.4	3.4	2.2
7	44.0	67.0	44.0	44.0	37.5	24.0	19.0	14.0	9.0	5.0	4.1
8	56.0	90.0	72.0	58.0	46.0	36.0	24.0	15.2	11.0	4.0	3.1
Average	49.0	68.9	60.4	50.7	39.2	30.2	22.7	13.7	10.5	5.1	3.3
Standard deviation	6.0	15.8	8.5	5.1	3.8	4.2	3.1	1.5	1.6	1.4	0.8

* V1 : 10 min sample at 11 min
V2 : 10 min sample at 11 min
V4 : 10 min sample at 11½ min
V5 : 45 min sample at 47 min

Tab E.7

Table II - HVT/80/2 - Part II

Percentage urinary recoveries of ceftazidime by MBA after an intravenous infusion of 1g ceftazidime over 20 min to 7 male volunteers

Volunteer Number	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1	55.3	17.1	9.6	3.4	85.4
2	54.1	17.8	10.1	2.6	84.6
3	44.8	19.6	9.1	2.1	75.6
4	49.4	15.5	9.1	4.6	78.6
5	54.3	19.8	10.5	1.5	86.1
7	45.9	18.3	12.4	4.3	80.9
8	60.6	19.2	11.4	3.5	94.7
Average	52.1	18.2	10.3	3.1	83.7
Standard deviation	5.6	1.9	1.2	1.2	6.2
Cumulative average	52.1	70.3	80.6	83.7	

Table IV - HVT/80/2 - Part II

Pharmacokinetic parameters of ceftazidime from MBA data after an intravenous infusion of 1g ceftazidime over 20 min to 7 male volunteers

Volunteer Number	Peak concentration (mg/l)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	74.0	18.5	141.9	117	100	1.8
2	74.0	18.7	149.6	111	94	1.9
3	75.0	20.0	140.2	119	90	1.9
4*	61.0*	21.1	156.1	107	84	2.3
5	64.0	20.1	123.9	134	116	1.7
7	67.0	24.1	133.8	125	101	2.2
8	90.0	16.0	156.8	106	100	1.7
Average	72.1	19.8	143.2	117	98	1.9
Standard deviation	9.6	2.5	12.0	10	10	0.2

* V4 : peak at 30 min

Table I - HVT/80/7

Serum levels of ceftazidime by MBA after an intravenous infusion of 2g ceftazidime over 20 min to 7 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) at time after dose:											
	10 min	20 min	30 min	45 min	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h
1	93.0	176.0	116.0	97.0	65.6	50.0	43.0	28.0	14.0	14.9	7.4	3.3
2	112.0	174.0	138.0	82.0	70.0	44.8	35.5	19.2	11.4	7.3	2.3	1.0
3*	138.0	32.0	156.0	90.0*	64.0	42.0	38.0	22.2	12.0	7.4	3.1	0.9
4	115.0	187.0	130.0	86.0	71.0	61.0	45.0	21.6	14.2	11.4	7.1	2.7
5	53.0	154.0	102.0	105.0	90.0	56.6	43.0	26.1	12.3	11.6	6.4	2.6
6	87.0	142.0	136.0	100.0	72.0	66.0	45.5	25.8	16.0	12.5	7.0	4.1
7+	102.0+	162.0	128.0	116.0	90.0	50.0	41.0	22.0	12.3	8.0	4.1	NS
Average	99.7	169.6	129.4	97.7	74.7	52.9	41.6	23.6	13.2	10.4	5.3	2.4
Standard deviation	29.1	17.9	17.1	12.5	10.9	8.6	3.7	3.1	1.6	2.9	2.2	1.3

* V3 : 45 min sample at 50 min

V7 : 10 min sample at 15 min

NS = No Sample

Table 27

Table II - HVT/80/7

Percentage urinary recoveries of ceftazidime by MBA after an intravenous infusion of 2g GR 20263 over 20 min to 7 male volunteers

Volunteer Number	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1*	49.3	21.8*	7.4*	4.5	83.0
2	58.7	19.1	9.5	2.2	89.5
3	58.3	16.5	7.6	2.5	84.9
4	53.5	18.7	9.3	3.9	85.4
5	58.1	19.4	12.9	4.4	94.8
6	51.9	15.9	11.3	4.8	83.9
7	57.8	19.1	8.5	2.8	88.2
Average	55.4	18.1	9.8	3.6	87.1
Standard deviation	3.8	1.5	2.0	1.1	4.1
Cumulative average	55.4	73.5	83.3	86.9	

* V1 : 2 - 4 h urine was 2 - 5 h
4 - 8 h urine was 5 - 8 h

223 062

Table IV - HVT/80/7

Pharmacokinetic parameters of ceftazidime from MBA data after an intravenous infusion of 2g ceftazidime over 20 min to 7 male volunteers

Volunteer Number	Peak concentration (mg/l)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	176.0	23.0	283	118	98	2.3
2	174.0	19.2	230	145	130	1.5
3	192.0	18.0	250	133	113	1.6
4	187.0	21.0	282	118	101	2.1
5	154.0	20.9	270	124	117	2.0
6	142.0	21.7	293	114	95	2.2
7	162.0	18.9	254	131	116	1.7
Average	170.0	20.4	266	126	110	1.9
Standard deviation	17.9	1.8	22	11	13	0.3

Table V - HVT/80/7

Clearance values for creatinine and ceftazidime after an intravenous infusion of 2g ceftazidime over 20 min to 7 male volunteers

MBA data

Volunteer Number	Creatinine Clearance (ml/min)	Renal Clearance ceftazidime (ml/min)	Renal Clearance Ratio ceftazidime/Creatinine
1	121	98	0.81
2	142	130	0.92
3	133	113	0.85
4	130	101	0.78
5	125	117	0.94
6	129	95	0.74
7	128	116	0.91
Average	130	110	0.85
Standard deviation	7	13	0.08

Table I - UVT/79/46

Serum levels of ceftazidime by MBA after an intramuscular injection of 500mg ceftazodime to 8 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) at time after dose:									
	15 min	30 min	45 min	1 h	1.5h	2 h	3 h	4 h	6 h	8 h
1	12.0	16.0	20.0	20.5	<u>21.5</u>	18.0	12.6	8.1	4.0	2.2
2	11.0	16.5	<u>19.5</u>	18.0	17.5	16.0	11.7	7.3	3.7	2.0
3	7.3	9.8	11.5	13.0	<u>13.5</u>	12.0	10.2	7.3	4.1	2.2
4	9.8	14.0	15.0	<u>17.0</u>	16.0	16.5	8.7	8.7	4.1	3.1
5	11.6	14.4	<u>16.2</u>	15.7	15.2	14.0	9.0	7.5	2.7	1.5
6	8.6	11.7	<u>16.0</u>	14.8	14.4	15.6	11.0	10.6	5.1	2.8
7	10.3	15.6	18.5	<u>20.2</u>	7.4	16.0	13.5	8.8	4.5	<1.5
8	13.6	14.2	15.2	<u>16.5</u>	11.8	14.7	13.0	8.8	4.5	<1.5
Average	10.5	14.0	15.5	17.0	16.3	15.4	11.2	8.4	4.1	2.3
Standard deviation	2.0	2.2	2.8	2.6	2.6	1.8	1.8	1.1	0.7	0.5

peak values underlined

(7)
Tab 3

Table II - HVT/79/46

Percentage urinary recoveries of ceftazidime by MBA after an intramuscular injection of 500mg ceftazidime to 8 male volunteers

Volunteer Number	% urinary recovery at hours after dose: 0 - 2	2 - 4	4 - 8	8 - 24	Total, 0 - 24 h %
1	30.5	36.5	19.3	4.2	90.5
2	33.8	28.3	16.0	6.0	84.1
3	31.7	23.9	20.1	4.0	79.7
4	49.5	23.2	16.6	5.7	95.0
5	37.8	24.1	20.3	4.5	86.7
6	24.5	25.7	23.2	6.3	79.7
7	37.2	23.9	18.7	6.6	86.4
8	24.7	25.4	19.2	5.5	74.8
Average	33.7	26.4	19.2	5.4	84.6
Standard deviation	8.1	4.4	2.2	1.0	6.5
Cumulative average	33.7	60.1	79.3	84.7	

Table IV - GVT/79/46

Compute · derived pharmacokinetic parameters of ceftazidime from MBA data after an intramuscular injection of 500mg to 8 male volunteers

Volunteer Number	Peak concentration (mg/l)	Time of peak concentration (h)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Renal clearance (ml/min)	Ultimate half-life (h)
1	21.3	1.1	14.9	82.1	101	92	1.7
2	19.1	1.0	18.6	76.8	109	91	2.0
3	13.3	1.3	26.0	67.5	124	99	2.4
4	16.9	1.1	21.3	76.5	109	103	2.3
5	16.6	0.9	22.9	68.6	121	105	2.2
6	15.9	1.2	23.4	87.1	96	76	2.8
7	19.4	1.1	18.1	86.0	97	84	2.2
8	16.7	0.8	24.8	87.4	95	71	2.2*
Average	17.4	1.1	21.2	79.0	106	90	2.2
Standard deviation	2.5	0.2	3.8	8.0	11	12	0.3

* derived from exponential regression (IPPE program) as this provided a better fit for the last points

223 090

Table V - HVT/79/46

Clearance values for creatinine and ceftazidime after an intramuscular injection of 500mg ceftazidime to 8 male volunteers

Volunteer Number	Creatinine Clearance (ml/min)	Renal Clearance ceftazidime (ml/min)	Renal Clearance Ratio ceftazidime/Creatinine
1	118	92	0.78
2	113	91	0.81
3	124	99	0.80
4	107	103	0.96
5	124	105	0.85
6	109	76	0.70
7	116	84	0.72
8	108	71	0.66
Average	115	90	0.78
Standard deviation	7	12	0.10

TABLE I - HVT/80/11

Urinary concentrations and percentage urinary recoveries of ceftazidime by MBA after an oral dose of 250mg ceftazidime to 7 male volunteers

Volunteer number	0-12h urinary concentration (mg/l)	0-12h urinary recovery (%)
1	1.2	0.4
2	1.9	0.4
4	0.7	0.2
5	0.6	0.4
6	<0.5	<0.4
7	1.6	0.4
8	2.8	0.6
Average	1.5	0.4

Table 35

Table I - HVT/80/9

Serum levels of ceftazidime by MBA after single and repeated intramuscular injections of 1g ceftazidime to 4 male volunteers

Dose 1

Volunteer Number	ceftazidime concentration (mg/l) at time after doses: 0	20 min	40 min	1 h	1.5h	2 h	3 h	4 h	6 h	8 h
1	0	14.0	23.0	54.0	30.0	31.0	27.5	21.5	10.8	7.4
3	0	~6.0	14.0	21.5	25.0	27.0	24.0	20.0	9.6	5.2
4	0	35.0	47.0	47.0	41.0	40.5	27.5	22.8	8.9	5.4
6	0	40.5	46.0	40.5	33.5	28.5	23.0	16.8	8.2	5.0
Average	0	29.8	32.5	40.8	32.4	31.8	25.5	20.3	9.4	5.8
Standard error		8.1	8.3	7.0	3.4	3.0	1.2	1.3	0.6	1.1

Dose 25

Volunteer Number	ceftazidime concentration (mg/l) at time after doses: 0	20 min	40 min	1 h	1.5h	2 h	3 h	4 h	6 h	8 h
1	0.7	38.5	38.0	40.0*	41.0	39.0	27.5	19.5	4.8	2.3
3	<0.6	24.2	30.0	27.0	29.0	29.0	27.5	21.5	5.1	2.6
4	0.8	29.0	35.0	49.0	39.0	40.0	32.5	27.0	8.3	4.3
6	<0.6	46.0	52.0	54.0	40.0	47.0	27.5	20.5	5.0	2.5
Average	0.7	34.4	38.8	43.3	37.2	38.8	28.8	22.1	5.8	2.9
Standard error		4.9	4.7	8.3	2.8	3.7	0.8	1.7	0.8	0.5

* V1 : 1 h sample taken at 1 h 8.5 min

peak values underlined

Table II - HVT/80/9

Peak serum levels of ceftazidime by MBA after intravenous injections of 1g ceftazidime over 20 min to 6 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) post-dose number: 1	2	3	19	20	21	28	29	30
7+	78.0*	94.0	81.0	93.0	100.6	94.0	84.0	69.0	112.0
8	76.0	78.0	88.0	91.0	106.0	100.0	86.0	90.0	98.0
9	78.0	96.0	105.0	84.0	104.0	100.0	94.0	94.0	81.0
10	86.0	81.0	82.0	80.0	104.0	88.0	102.6	112.0	102.0
11	98.0	100.0	106.0	110.0	104.0	110.0	110.0	124.0	153.0
12	70.0	94.0	105.0	92.0	108.6	104.0	77.6	114.0	98.0
Average	81.6	90.5	94.5	91.7	104.5	99.3	92.4	100.5	107.3
Standard error	4.8	3.6	4.9	4.2	1.1	3.1	5.0	8.2	10.0

+ V7 : dose 1 given over 10 min instead of 20 min

Table III - HVT/80/9

Trough serum levels of ceftazidime by MBA before successive intravenous injections of 1g ceftazidime to 6 male volunteers

Volunteer Number	ceftazidime concentration (mg/l) pre-dose number: 1	2	3	4	19	20	21	22	28	29	30	12 h post-dose 30
7*	0	7.4	9.4	<0.6	129.0*	7.9	10.0	0	<0.8	4.9	6.0	<0.8
8	0	7.0	8.5	<0.6	0	7.3	9.8	0	<0.8	2.9	4.4	<0.8
9	0	7.3	10.0	<0.6	0	7.1	8.4	0	<0.8	4.1	4.5	<0.8
10	0	4.4	5.4	1.8	0	4.6	5.7	0	<0.8	3.0	3.2	<0.8
11	0	11.2	14.0	0.6	0	9.6	11.0	<3	<0.8	4.7	7.8	<0.8
12	0	7.6	8.4	<0.6	0	8.6	9.1	0	<0.8	4.1	4.6	<0.8
Average	0	7.5	9.3	0.8	0	7.5	9.0	0	<0.8	4.0	5.4	<0.8
Standard error	0	0.9	1.1	-	0	0.7	0.8	-	0	0.3	0.8	0

* V7 : pre-dose 19 value inexplicable; left out of average

Table IV - HVT/80/9

Computer derived pharmacokinetic parameters of ceftazidime from MBA data after 1 and 25 intramuscular injections of 1g ceftazidime to 4 male volunteers

Dose 1

Volunteer Number	Peak concentration (mg/l)	Time of peak concentration (h)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Ultimate half-life (h)
1	36.6	1.4	17.7	181	92	2.2
3	25.5	2.1	14.4	145	115	1.4
4	47.6	0.9	15.8	203	82	2.2
6	44.3	0.6	19.0	169	99	2.2
Average	38.5	1.2	16.7	174	97	2.0
Standard error	4.9	0.3	1.0	12	7	0.2

Dose 25

Volunteer Number	Peak concentration (mg/l)	Time of peak concentration (h)	Apparent volume of distribution (l)	Area under serum level/time curve (mg/l.h)	Plasma clearance (ml/min)	Ultimate half-life (h)
1	44.5	0.9	16.8	180	92	2.1
3	32.2	1.2	22.7	162	103	2.5
4	44.7	1.2	14.9	204	82	2.1
6	54.6	0.8	14.0	199	84	1.9
Average	44.0	1.0	17.1	186	90	2.2
Standard error	4.6	0.1	2.0	10	5	0.1

Table I - HVT/80/26

Serum levels of ceftazidime after a (slow) bolus intravenous injection of 2g to 8 male volunteers.

Dose 1

Volunteer Number	ceftazidime concentration (mg/l) at time after dose: 10min	15min	30min	45min	1h	1.5h	2h	3h	4h	6h	8h
1	123.6	162.0	95.6	125.6	64.2	57.8	38.9	21.0	15.5	14.3	6.6
2	192.2	111.0	92.8	94.2	83.0	54.2	30.0	22.0	19.2	18.0	7.1
3	175.0	145.6	106.0	96.6	97.4	59.4	37.9	23.2	12.9	9.0	5.2
4	163.8	176.2	145.6	111.8	101.8	77.4	38.7	25.4	17.3	12.0	6.3
5	248.0	137.6	106.8	88.2	92.2	63.6	31.0	27.6	11.6	9.9	4.9
6	226.0	152.2	132.0	117.2	84.6	59.0	37.0	22.5	15.3	9.8	6.1
7	151.2	99.8*	109.8	80.0*	60.6	43.4	31.2	22.2	16.5	9.3	4.3
8	222.0*	173.6	118.2	102.8	92.4	56.4*	38.0	21.2	12.9	8.1	2.1
Average	182.8	151.2	113.4	105.2	85.5	59.2	35.3	23.1	15.2	11.3	5.3
Standard Error	16.3	8.6	6.4	5.1	4.7	3.9	1.4	0.8	0.9	1.2	0.6

*V8: 10 min sample at 11 min *V7: 45 min sample at 46 min
*V7: 15 min sample at 16 min *V8: 1.5h sample 4 min late

Asterisked values have been excluded from calculations of means and standard errors throughout.

Table II - HVT/80/26

Serum levels of ceftazidime after a (slow) bolus intravenous injection of 2g to 7 male volunteers.

Dose 28

Volunteer Number	ceftazidime concentration (mg/l) at time after dose: 0 min	10min	15min	30min	45min	1h	1.5h	2h	3h	4h	6h	8h
1	Withdrawn from Trial											
2	3.3	127.0	180.6	132.2	89.6	72.8	56.2	42.8	30.5	23.0	11.6	6.2
3	1.9	150.2	121.4	95.0	77.0	85.4	65.4	39.8	25.6	15.2	7.9	3.7
4	4.8	144.6	151.6	94.2	91.2	70.4	61.4	49.0	35.1	25.6	10.6	6.0
5	1.6	126.8	114.0	91.8	91.2	68.2	56.2	44.6	26.7	18.3	<1.6	3.8
6	3.0	196.8	192.4	97.0	98.6	85.0	31.2	59.9	35.6	23.1	10.3	4.8
7	1.6	182.4	130.8	84.4	97.4	81.4	64.8	46.2	28.9	19.5	8.6	4.2
8	2.1	169.0	152.8	104.6	120.2	76.6	57.2	47.7	28.1	17.4	5.3	3.5
Average	2.6	156.7	149.1	99.9	95.0	77.1	63.2	47.1	30.1	20.3	9.1	4.6
Standard Error	0.4	10.2	11.1	5.8	5.0	2.6	3.3	2.4	1.5	1.4	0.9	0.

120 422.

Table III - HVT/80/26

Percentage urinary recoveries of ceftazidime after an intravenous injection of 2g ceftazidime to 8 male volunteers.

After Dose 1

Volunteer Number	% urinary recovery at hours after dose: 0 - 2h	2 - 4h	4 - 8h	Total 0 - 8h (%)
1	59.9	13.9	12.9	86.7
2	49.2	11.1	29.2	89.5
3	52.8	18.5	9.9	81.2
4	46.4	22.7	12.7	81.8
5	45.3	24.5	9.3	79.1
6	48.8	8.7	17.1	74.6
7	45.3	17.2	13.1	75.6
8	47.7	17.8	15.3	80.8
Average	49.4	16.8	15.9	81.2
Standard Error	1.7	1.9	2.2	1.8
Cumulative Average	49.4	66.2	81.1	

Table IV - HVT/80/26

Percentage urinary recoveries of ceftazidime after an intravenous injection of 2g ceftazidime to 7 male volunteers.

After Dose 28

Volunteer Number	% urinary recovery at hours after dose: 0 - 2h	2 - 4h	4 - 8h	Total 0 - 8h (%)
1		Withdrawn		
2	42.8	20.4	13.5	76.7
3	48.1	16.3	10.2	74.6
4	43.1	18.2	12.7	74.0
5	43.9	15.2	10.4	69.5
6	49.3	8.8	18.2	76.3
7	47.2	19.3	17.2	83.7
8	54.9	14.5	9.7	79.1
Average	47.0	16.1	13.1	76.3
Standard Error	1.6	1.5	1.3	1.7
Cumulative Average	47.0	63.1	76.2	

Table V - HVT/80/26

Trough serum levels of ceftazidime after intravenous injections of 2g ceftazidime to 8 male volunteers.

Volunteer Number	ceftazidime concentration (mg/l) before dose number: 2	3	4	5	6	8
1	6.6	10.2	7.0	7.2	7.9	9.2
2	7.1	7.9	10.3	7.6	7.3	7.4
3	5.2	6.8	7.3	6.1	5.8	6.2
4	6.3	9.1	10.6	8.8	7.5	9.8
5	4.9	7.9	5.6	6.9	6.3	6.2
6	6.1	11.2	9.2	7.7	8.8	9.5
7	4.3	NS	7.2	6.1	6.8	7.2
8	2.1	6.8	7.8	7.1	6.8	8.0
Average	5.3	8.6	8.1	7.2	7.2	7.9
Standard Error	0.6	0.6	0.6	0.3	0.3	0.5

NS = No sample

Table VII - HVT/80/26

Pharmacokinetic parameters of ceftazidime after an intravenous (slow) bolus injection of 2g to 8 male volunteers.

Dose 1

Volunteer Number	Apparent Volume of Distribution (l)	Area Under Serum level/ Time Curve 0 - ∞ (mg/l.h)	Total Clearance (ml/min)	Area Under Serum level/ Time Curve 0-8h (mg/l.h)	Renal Clearance (ml/min)	Drug/ Creatinine Clearance Ratio	Time above 8mg/l (min)	Ultimate Half-l. (h)
1	23.0	280.5	119	260.5	111	1.06	430	2.2
2	23.8	289.9	115	268.9	113	0.65	460	2.4
3	18.6	271.9	123	261.7	103	0.91	377	1.8
4	16.7	320.0	104	305.9	89	0.90	413	1.8
5	18.5	275.2	121	264.8	100	0.62	376	1.8
6	18.9	294.6	113	281.0	87	0.91	397	1.9
7	23.2	237.5	140	226.0	112	0.84	371	1.9
8	15.2	265.5	126	261.1	103	0.71	324	1.4
Average	19.7	279.4	120	265.7	102	0.82	394	1.9
Standard Error	1.1	8.5	4	7.9	4	0.05	15	0.1

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Table VIII - HVT/80/26

Pharmacokinetic parameters of ceftazidime after an intravenous (slow) bolus injection of 2g to 7 male volunteers.

Dose 28

Volunteer Number	Apparent Volume of Distribution (l)	Area Under Serum level/ Time Curve 0 - ∞ (mg/l.h)*	Total Clearance (ml/min)	Area Under Serum level/ Time Curve 0-8h (mg/l.h)+	Renal Clearance (ml/min)	Drug/ Creatinine Clearance Ratio	Time above 8mg/l (min)	Ultimate Half-li (h)
1			withdrawn from trial					
2	20.03	291.4	114	283.8	90	0.77	427	2.0
3	18.29	248.7	134	245.7	101	0.77	357	1.6
4	19.50	283.9	117	281.4	88	0.84	424	1.9
5	19.70	245.5	136	240.5	96	0.70	367	1.7
6	14.78	318.4	105	314.8	81	0.82	400	1.6
7	17.39	272.0	123	266.7	105	0.69	376	1.6
8	16.41	263.3	127	261.7	101	0.83	344	1.5
Average	18.0	274.7	122	270.7	95	0.77	385	1.7
Standard Error	0.7	9.7	4	9.6	3	0.02	12	0.1

* Does not include that fraction contributed by drug remaining from dose 27

+ Includes fraction contributed by drug remaining from dose 27

Table IX - HVT/80/26

Serum creatinine levels (and creatinine clearances) after an intravenous (slow) bolus injection of 2g ceftazidime to 8 volunteers; comparison after 1, 12 and 28 doses.

Volunteer Number	Plasma Creatinine (µmol/l) (creatinine clearance, ml/min) After 1 dose	After 12 doses	After 28 doses
1	106 (105)	104	NA (-)
2	102 (175)	112	107 (117)
3	90 (113)	91	80 (132)
4	116 (99)	117	105 (104)
5	81 (162)	92	81 (
6	114 (96)	115	111
7	101 (134)	116	102 (
8	82 (145)	87	80 (121)
Average	99 (129)	104	95 (123)
Standard Error	5 (11)	4	5 (7)

NA = Not assessed

(11)
Table 47

Parameter	Group receiving	
	15mg/kg	30mg/kg
Serum concentration at 30 minutes	37.8 mg/l	186.4 mg/l
Ultimate serum half-life	1.85 h	1.72 h
Volume of distribution	0.73 l/kg	0.52 l/kg
Total clearance	5.03 ml/min/kg	3.75 ml/min/kg

✓

These compare with healthy adult male volunteers receiving 1g and 2g infusions as follows:

Parameter	Group receiving	
	1g	2g
Serum concentration at 30 minutes	60.4 mg/l	129.4 mg/l
Ultimate serum half-life	1.9 h	1.9 h
Volume of distribution	0.26 l/kg	0.28 l/kg
Total clearance	1.54 ml/min/kg	1.70 ml/min/kg

Norrby et al (1g ceftazidime three times daily)

Patient number	Age (years)	dose 1		after 3-6 days	
		Cl-EDTA (ml/min)	CAZ half-life (h)	Cl-EDTA (ml/min)	CAZ half-life (h)
3	73	107	1.3	97	1.5
6	77	92	1.9	66	2.5
7	79	76	1.9	72	2.5
9	82	69	2.9	57	2.1
10	77	64	2.3	65	2.4
11	84	60	1.8	52	2.9
12	78	54	3.2	47	3.5
14	78	47	3.7	48	2.9

Alestig et al (2g ceftazidime twice daily)

Patient number	Age (years)	Cl-EDTA (ml/min)	CAZ half-life (h)	Day of treatment
B091	89	49	4.4	7
B117	85	31	3.5	8
B119	70	116	1.8	9
B119	70	111	1.5	8
B186	79	48	2.7	10
B188	77	6	10.5	21
B111	73	35	6.1	10

The mean volume of distribution and clearance of ceftazidime for non-cystic patients was smaller than that found for the cystic patients. However, the differences do not appear to be of clinical significance.

Table 3

Pharmacokinetic Summary

Non-Fibrocystic Patients

Demographics			Serum Concentrations (mg/L)								Pharmacokinetic Paramet		
Patient #	Age	Wt (kg)	0 min	15 min	30 min	45 min	1 hr	2 hr	4 hr	6 hr	Half-Life	Clear-ance	Vol Dis
4	1m	4.5	0	145	60	-	54	40	15.8	1.4	1.0	0.267	3.
5	2y	11.8	0	177	73	-	48	35	26	-	*	*	*
7	11y	37.6	0.5	180	125	-	72	32	12.8	3.6	1.2	0.226	3.
9	2m	5.4	0.3	168	103	77	49	36	18	6	1.7	0.23	3.
61	16m	6.3	0	98	92	4	-	-	12.3	-	*	*	*
											1.3	.241	.
Mean	2.9	13.1									.1	.01	.
SEM	2.1	6.4											

Table 4

Pharmacokinetic Summary

Fibrocystic Patients

Demographics			Serum Concentrations (mg/L)								Pharmacokinetic Paramet		
Patient #	Age	Wt (kg)	0 min	15 min	30 min	45 min	1 hr	2 hr	4 hr	6 hr	Half-Life	Clear-ance	Vol Di
1	3y	11.3	0	200	-	46	43	24	10.4	2.3	1.2	0.410	0.
2	10y	18.1	0	128	90	57	47	24	10.4	2.3	1.2	0.403	0.
3	8y	20.3	0	178	113	79	40	17	2.7	1.1	0.9	0.523	0.
6	5m	5.4	0.4	163	-	-	64	40	14.2	5	1.4	0.342	0.
8	3y	12.7	0	224	125	-	72	30	5	2.2	1.0	0.358	0
											1.1	.408	
Mean	4.9	13.7									.1	.03	
SEM	1.8	2.7											

Table 3

Summary Table

Ceftazidime

Serum Concentrations (mg/L)

Patient	Age	Wt (kg)	Dose (mg)	0 min	15 min	30 min	60 min	2 hr	4 hr	8 hr	T 1/2	AUC	VD (L/kg)	TBC (L/hr/kg)
101	1d	1.8	60	70.3	55.8	65.8	62.5	63.6	46.9	32.4	6.9	395	0.8	0.08
105	9d	1.3	38	(277)	(99.2)	(66.2)	(53.7)	(52.7)	(46.1)	(36.4)	Peripheral vascular collapse			
102	3d	2.7	75	65.9	65.9	64.7	55.8	44.6	35.7	17.9	4.4	301	0.6	0.10
106	2d	2.7	75	101.6	73.8	60.4	53.7	42.4	38.3	21.1	5.5	314	0.8	0.10
100	1d	2.6	75	76.0	90.0	87.0	61.0	64.0	44.0	24.0	4.8	386	0.5	0.8
109	3d	3.0	90	125	78.9	61.7	56.6	45.5	29.3	17.2	4.1	291	0.6	0.10
110	5d	2.7	75	88	49.5	40.4	34.4	26.3	17.2	6.1	2.8	168	0.7	0.18
107	5d	1.8	56	137.7	97.7	84.7	72.9	56.5	32.9	21.1	4.0	354	0.5	0.09
113	2d	1.36	36	101	71.2	71.2	65.7	53.5	49.5	31.3	6.9	398	0.8	0.08
103	2d	2.7	80	121.6	73.7	68.1	57.0	50.2	38.8	21.0	4.8	330	0.6	0.09
104	2d	3.6	100	77.7	63.3	59.4	50.8	40.3	25.0	10.6	3.1	243	0.5	0.12
Mean	3.7	2.3	69.1	96.5	72.0	66.3	57.0	48.7	35.6	20.3	4.7	318	0.6	0.10
SEM	0.8	0.2	6.0	7.9	4.6	4.1	3.2	3.6	3.2	2.6	.4	23.0	0.04	0.01

( ) - Data not included in mean and standard error calculations

Creatinine clearance (number of patients)	Half-life (h)	Area under curve (o-∞) mg/l.h	Total volume of distrib-ution (l)	Urinary recovery (%) (collec-tion time)
>80 ml/min (5)	1.5	133	17.8	84 (24h)
30-80 ml/min (5)	3.6	318	17.5	62 (48h)
13-29 ml/min (6)	9.0	788	16.1	51 (48h)
2-12 ml/min (4)	16.1	1173	19.1	37 (48h)
<2 ml/min (4)	25.5	2343	14.2	-
<2ml/min on haemodialysis (4)	2.8	NA	NA	-

NA - not applicable

TABLE 1

PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME IN HEALTHY VOLUNTEERS

FOLLOWING A 1G BOLUS INJECTION

No.	A (μg/ml)	α (h^{-1})	$t_{\frac{1}{2}}\alpha$ (h)	B (μg/ml)	β (h^{-1})	$t_{\frac{1}{2}}\beta$ (h)	$AUC^{0-\infty}$ (μg/ml.h)	Total Body Clearance (ml/min)	V_D (l)	Dose of CAZ given (mg)	Amount Recovered in urine in 24h (% of dose)
1	70.8	4.31	0.16	46.6	0.470	1.47	116	143	18.2	990	82
2	119.9	7.03	0.10	57.3	0.456	1.52	143	120	16.0	1095	63
3	43.4	3.88	0.18	59.5	0.442	1.57	146	134	18.2	1170	89
4	69.2	2.99	0.23	48.9	0.393	1.76	148	108	16.5	960	85
5	67.3	6.40	0.11	52.5	0.514	1.35	113	166	19.4	1125	79
Mean	74.1	4.92	0.16	53.0	0.455	1.53	133	136	17.8	1068	84
SD	27.9	1.72	0.05	5.4	0.044	0.15	17	21	1.2	90	4

TABLE II

PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME IN PATIENTS WITH IMPAIRED RENAL FUNCTION (Cr Cl 30-80ml/min) FOLLOWING A 1g BOLUS INJECTION

No.	A (μg/ml)	α (h^{-1})	$t_{\frac{1}{2}\alpha}$ (h)	B (μg/ml)	β (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	$AUC^{0-\infty}$ (μg/ml.h)	Total Body Clearance (ml/min)	V_D (l)	Corrected Cr Cl (ml/min)	Dose of CAZ given (mg)
6	33.3	6.02	0.12	51.9	0.162	4.28	326	48	18.0	39	948
7	84.7	7.04	0.10	53.5	0.221	3.14	254	73	19.9	72	1119
8	11.2	3.48	0.20	55.0	0.153	4.53	363	52	20.3	39	1125
9	56.2	4.83	0.14	70.6	0.223	3.11	328	63	16.9	73	1241
10	171.7	8.45	0.08	66.8	0.225	3.08	317	47	12.6	69	900
Mean	71.4	5.96	0.13	59.6	0.197	3.63	318	57	17.5	58	1067
SD	62.3	1.92	0.05	8.5	0.036	0.72	40	11	3.1	18	140

TABLE III

PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME IN PATIENTS WITH IMPAIRED RENAL FUNCTION (Cr Cl 10-30ml/min) FOLLOWING A 1g BOLUS INJECTION

No.	A (μg/ml)	α (h^{-1})	$t_{\frac{1}{2}\alpha}$ (h)	B (μg/ml)	β (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	$AUC^{0-\infty}$ (μg/ml.h)	Total Body Clearance (ml/min)	V_D (l)	Corrected Cr Cl (ml/min)	Dose of CAZ given (mg)
11	87.1	3.66	0.19	66.6	0.097	7.15	710	21	12.7	27	870
12	81.3	7.37	0.09	62.1	0.077	9.00	818	17	13.3	14	840
13	63.6	1.36	0.51	69.9	0.073	9.50	1004	19	15.3	25	1125
14	113.9	7.39	0.09	58.8	0.077	9.00	779	22	17.1	21	1023
15	34.5	5.30	0.13	52.5	0.077	9.50	600	21	16.0	18	840
16	54.0	2.69	0.26	49.4	0.070	9.90	726	26	22.1	23	1125
Mean	72.4	4.63	0.21	59.9	0.079	9.00	708	21	16.1	21	973
SD	27.8	2.49	0.16	7.9	0.010	0.97	116	3	3.4	5	135

TABLE IV

PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME IN A PATIENT WITH IMPAIRED RENAL FUNCTION (Cr Cl 6ml/min) FOLLOWING A 1g BOLUS INJECTION

No.	A (μg/ml)	α (h^{-1})	$t_{\frac{1}{2}\alpha}$ (h)	B (μg/ml)	β (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	$AUC^{0-\infty}$ (μg/ml.h)	Total Body Clearance (ml/min)	V_β (l)	Corrected Cr Cl (ml/min)	Dose of CAZ given (mg)
17	51.4	1.68	0.41	63.9	0.044	15.75	1483	10	13.3	6	870

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Cont. 55

TABLE V

PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME IN ANURIC PATIENTS

FOLLOWING A 1g BOLUS INJECTION

No.	A (μg/ml)	α (h^{-1})	$t_{\frac{1}{2}}\alpha$ (h)	B (μg/ml)	β (h^{-1})	$t_{\frac{1}{2}}\beta$ (h)	$AUC^{0-\infty}$ (μg/ml.h)	Total Body Clearance (ml/min)	V_D (l)	Corrected Cr Cl (ml/min)	Dose of CAZ given (mg)
18	23.6	2.47	0.28	55.4	0.025	27.7	2226	7	17.9	0	996
19	36.8	2.68	0.26	72.6	0.026	26.7	2806	6	13.6	0	990
20	17.3	2.29	0.30	65.4	0.037	18.7	1775	6	9.3	0	609
21	22.8	9.93	0.07	61.5	0.024	28.9	2565	6	15.9	0	981
Mean	25.1	4.34	0.23	63.7	0.028	25.5	2343	6.3	14.2	0	894
SD	8.3	3.73	0.11	7.2	0.006	4.6	447	0.5	3.7	0	190

Table 57

(Dr. George)

Pharmacokinetic Summary Table

Group	n	Normalized Creatinine Clearance (ml/min/1.73M^2)	Beta Half-Life (hr)	Normalized Total Body Clearance (ml/min/1.73M^2)	VDSS (L/kg)
I	6	119 ± 10	1.7 ± 0.1	106 ± 5	0.19 ± 0.01
II	1	39	8.5	28	0.25
III	2	23 ± 3	13.0 ± 4.8	21 ± 6	0.30 ± 0.02
IV	3	10 ± 2	21.3 ± 4.4	10 ± 1	0.25 ± 0.04
V	6	0	30.8 ± 2.4	7 ± 1	0.24 ± 0.02

(Dr Acchiardo)

Pharmacokinetic Summary Table

Group	n	Normalized Creatinine Clearance[a]	Normalized Total Body Clearance[a]	Beta T 1/2[b]	VDSS[c]
I	8	111.1 ± 8	115.0 ± 16	2.1 ± 0.34	0.225 ± 0.01
II	3	45.9 ± 5.5	32.2 ± 5.1	4.7 ± 0.85	0.165 ± 0.007
III	3	19.8 ± 1.7	19.1 ± 3.1	11.3 ± 2.9	0.215 ± 0.028
IV	6	12.9 ± 1.0	11.7 ± 1.1	15.4 ± 2.7	0.210 ± 0.025
V	6	0.00	4.9 ± 0.6	32.2 ± 2.2	0.212 ± 0.026

[a] = ml/minute/1.73 [b] = hr [c] = L/kg

TABLE 3

PREDICTED CA2 CONCENTRATIONS FOR VARIOUS RENAL FUNCTIONS[a]

$t_{\frac{1}{2}\beta}$	CREATININE CLEARANCE NORMALIZED	1000mg q 8hr		1000mg q 12hr		1000mg q 24hr		500mg q 12hr		500mg q 24hr		500mg q 48hr	
		CSSMAX	CSSMIN	CSSMAX	CSSMIN	CSSMAX	CSSMIN	CSSMAX	CSSMIN	CSSMAX	CSSMIN	CSSMAX	CSSMIN
1.6[d]	120[c]	62.6[b]	2.2										
2.1	100	67.1	5.5	63.7	1.4								
2.8	80	73.8	11.3	67.2	3.8	64.0	0.2						
3.8	60	84.6	21.0	72.8	8.7	65.6	0.9	36.4	4.3				
4.4	50	91.5	28.3	77.1	12.8	66.9	1.7	38.6	6.4	33.4	0.8		
5.4	40	102.3	39.0	83.6	19.0	68.9	3.4	41.8	9.5	34.4	1.7	32.9	0.1
6.9	30			94.7	30.0	72.8	6.9	47.4	15.0	36.4	3.5	33.1	0.3
9.8	20					81.8	15.6	58.5	26.9	40.9	7.8	34.5	1.2
16.2	10							83.7	51.2	52.1	19.2	38.5	5.1
22.2	5									65.6	30.6	45.3	9.8

[a]Based on a 30 minute infusion in a 70 kg patient with a VDSS of 0.21 L/kg.

[b]mg/L

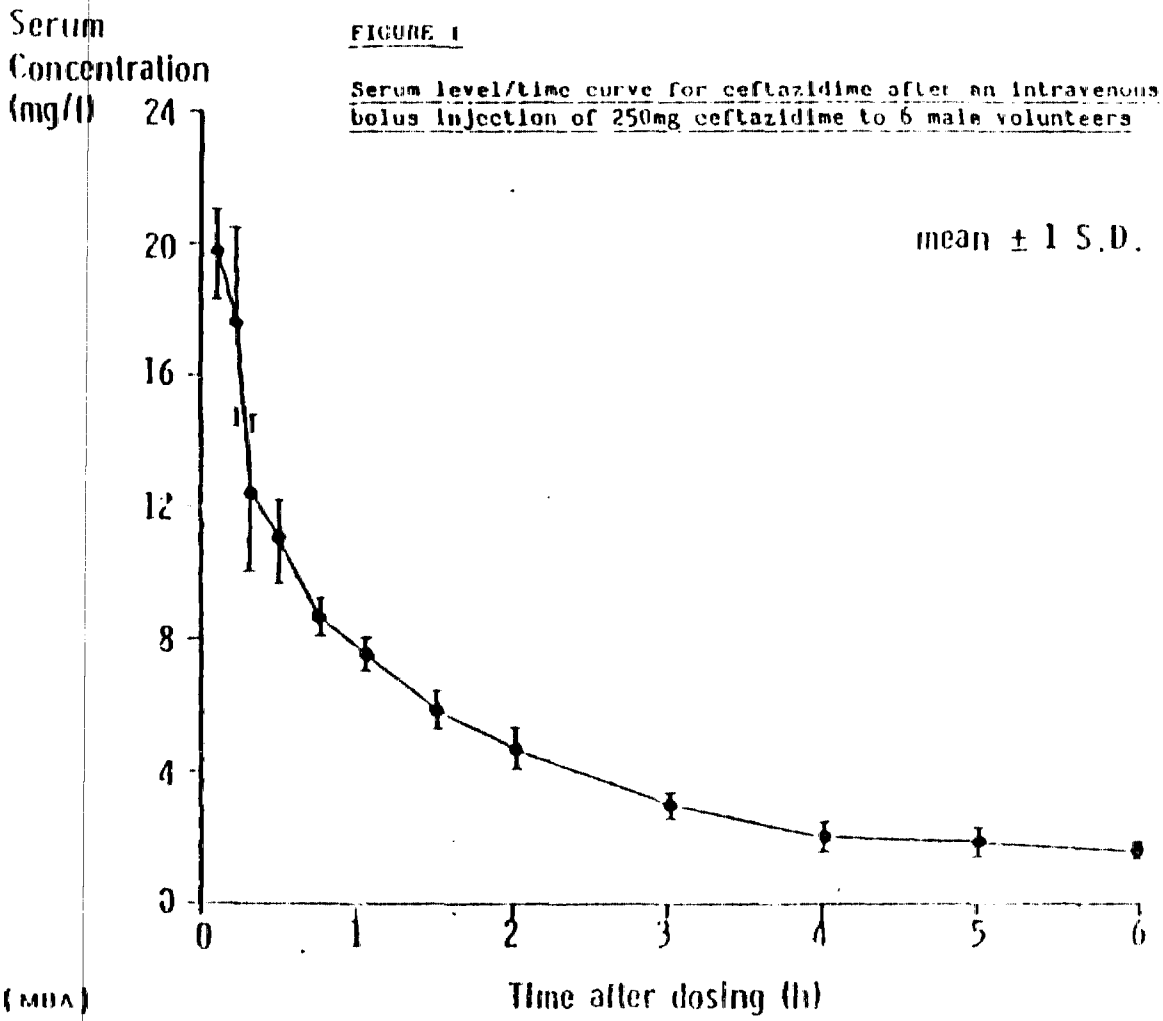
[c]ml/min/1.73M^2

[d]From: $t_{\frac{1}{2}\beta} = 22.7e^{.097Cl_{cr}} + 8.73e^{.014Cl_{cr}}$

Tab 2a, 5a

FIGURE 1

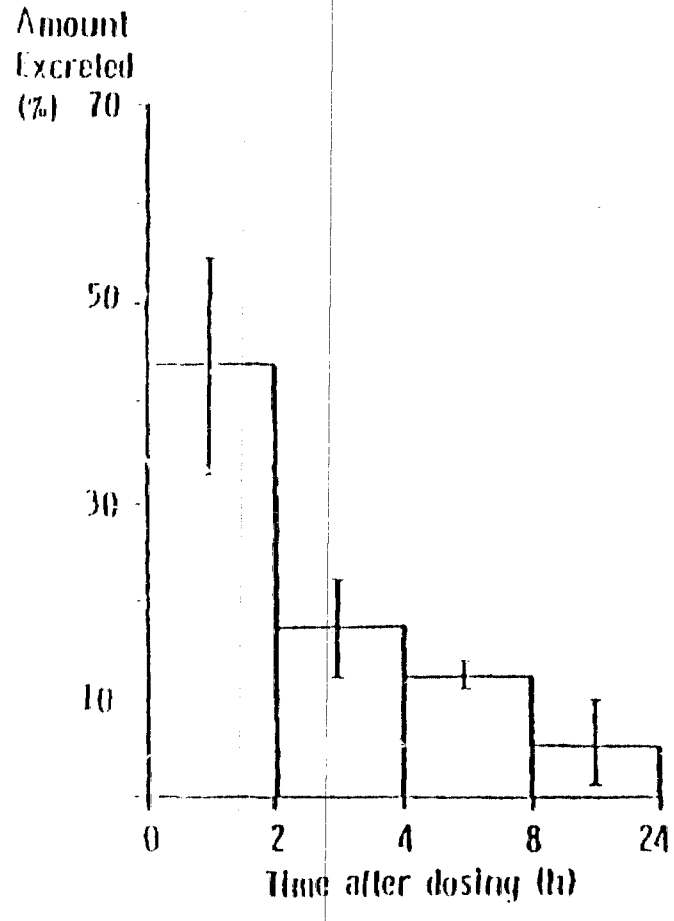
Serum level/time curve for ceftazidime after an intravenous bolus injection of 250mg ceftazidime to 6 male volunteers



(MDA)

FIGURE 2

Urinary excretion of ceftazidime after an intravenous bolus injection of 250mg ceftazidime to 6 male volunteers (MBA)



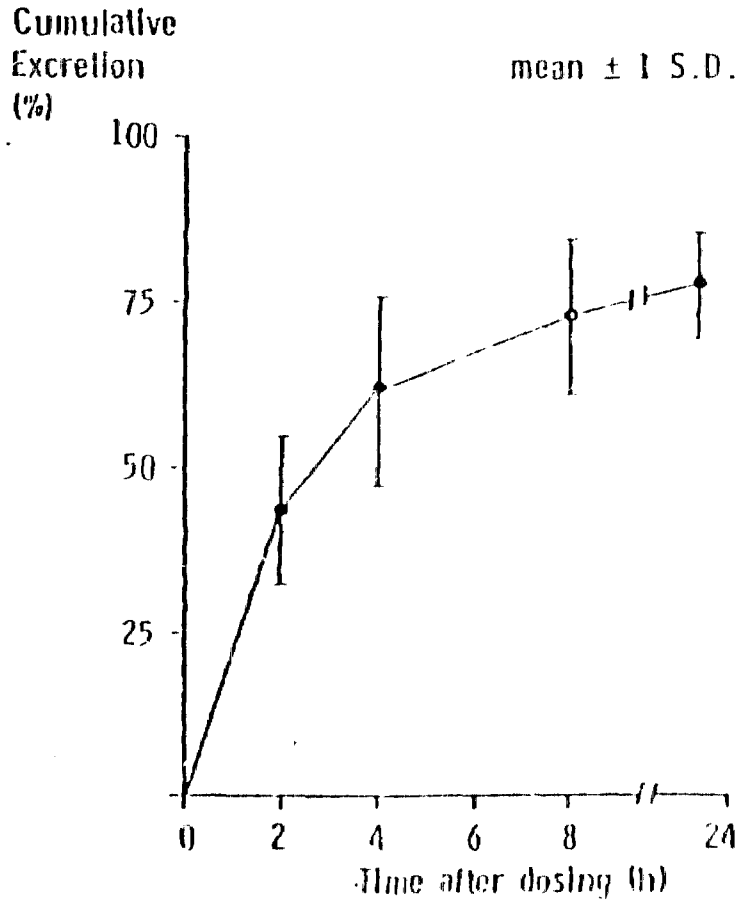
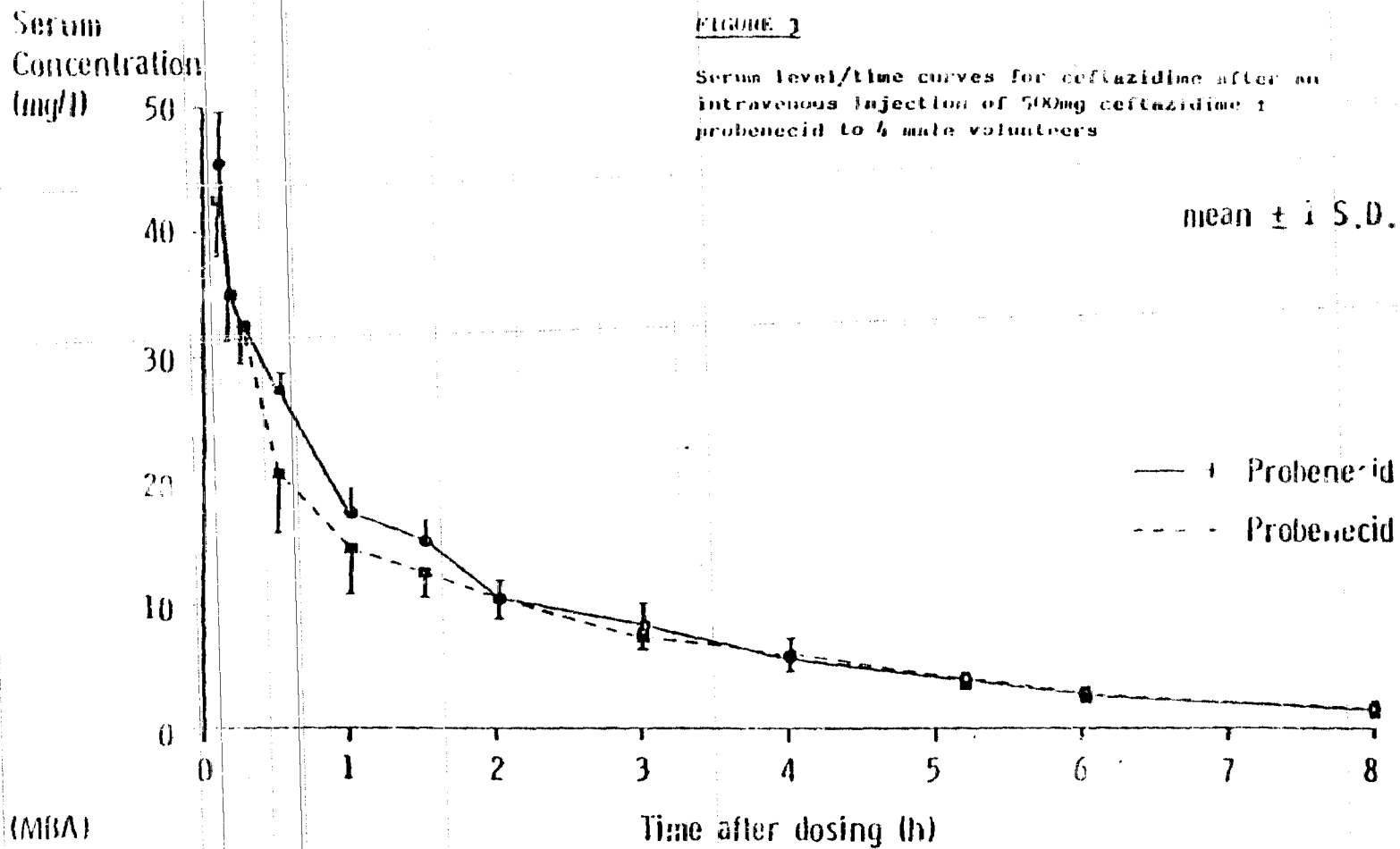


FIGURE 1

Serum level/time curves for ceftazidime after an intravenous injection of 500mg ceftazidime ± probenecid to 4 male volunteers



(MBA)

FIGURE 4

Urinary excretion of ceftazidime after an intravenous injection of 500mg ceftazidime to 4 male volunteers (MHA)

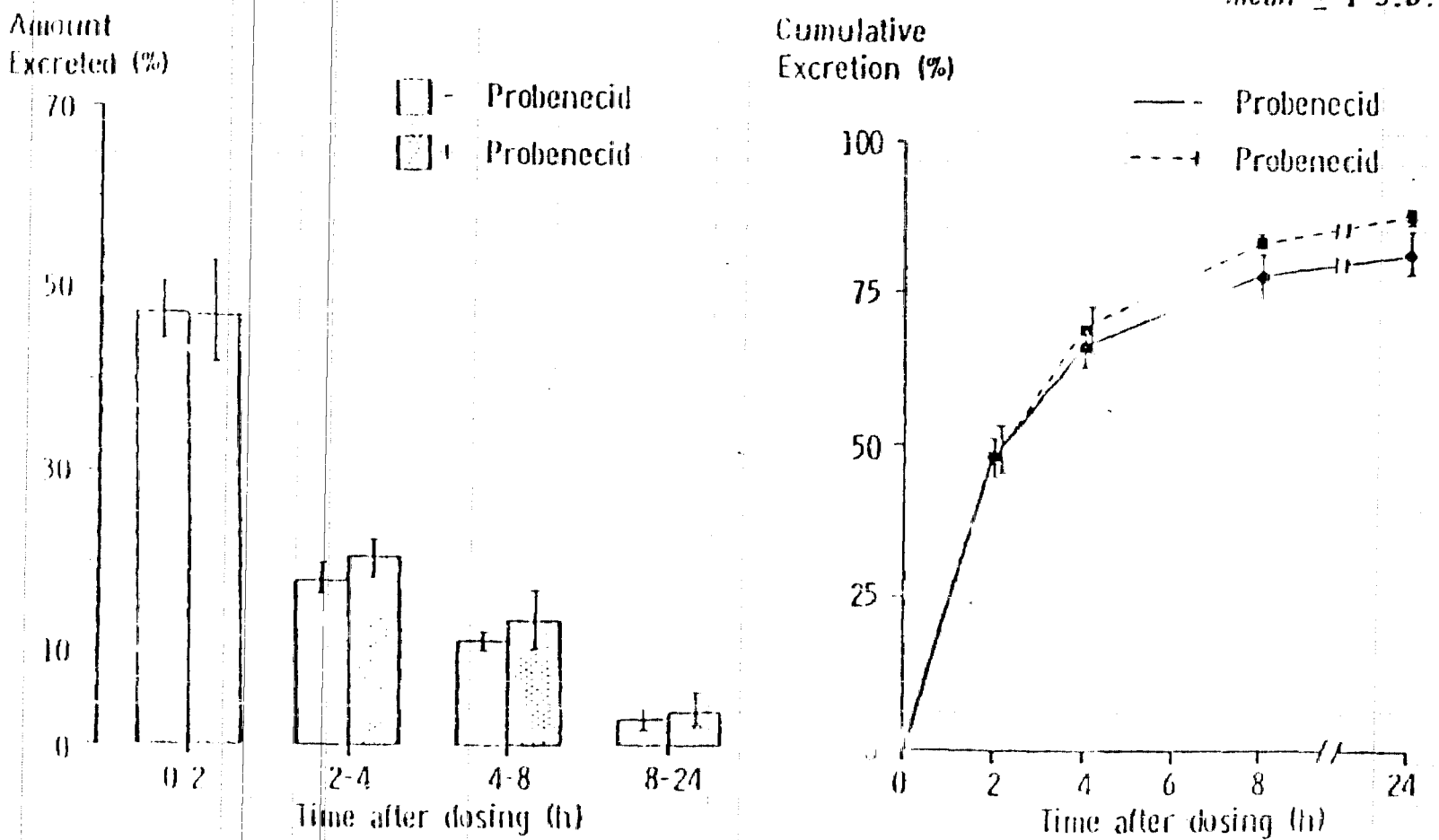
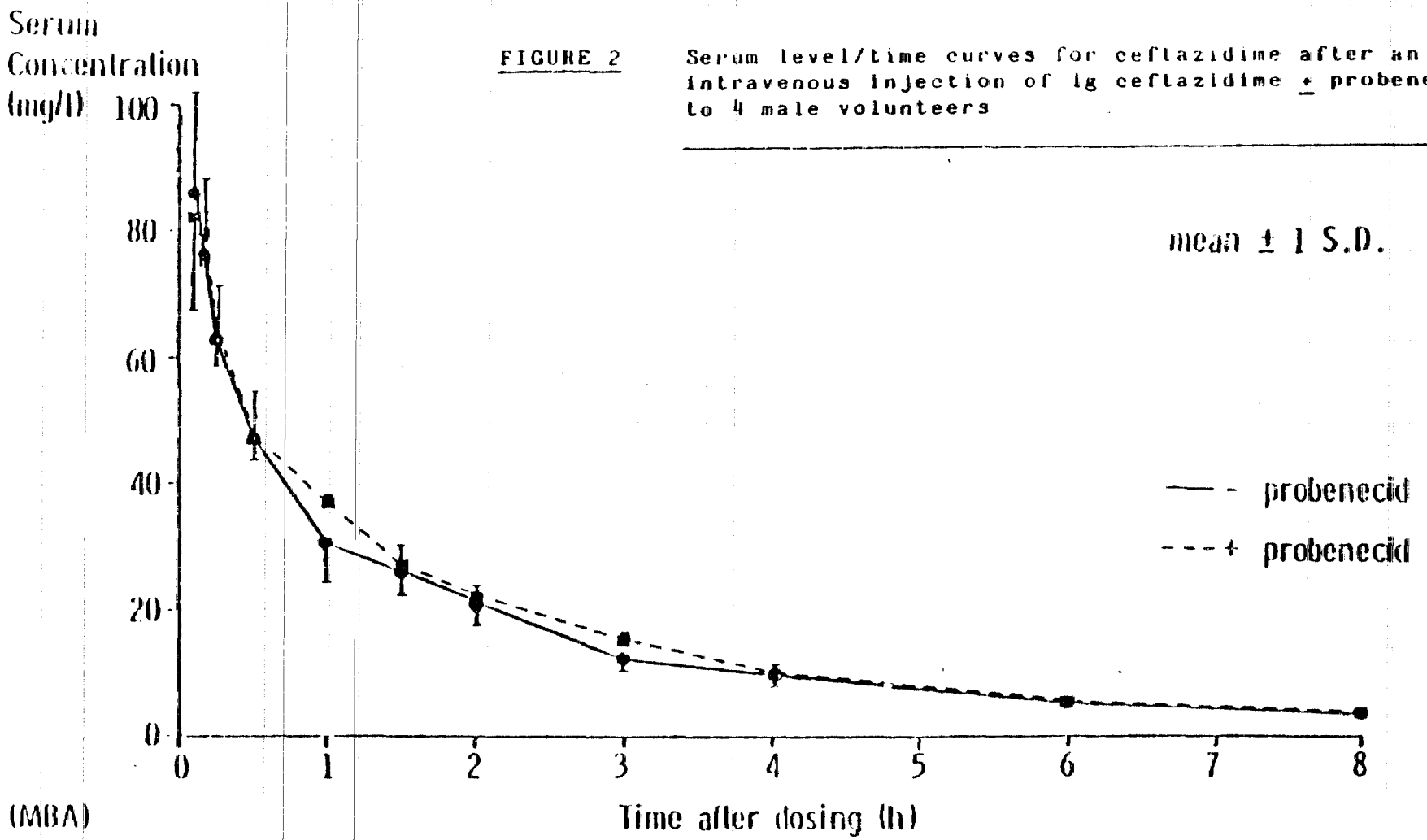


FIGURE 2 Serum level/time curves for ceftazidime after an intravenous injection of 1g ceftazidime ± probenecid to 4 male volunteers



(MBA)

FIGURE 5

Urinary excretion of ceftazidime after an intravenous injection of 1g ceftazidime to 4 male volunteers (MBA)

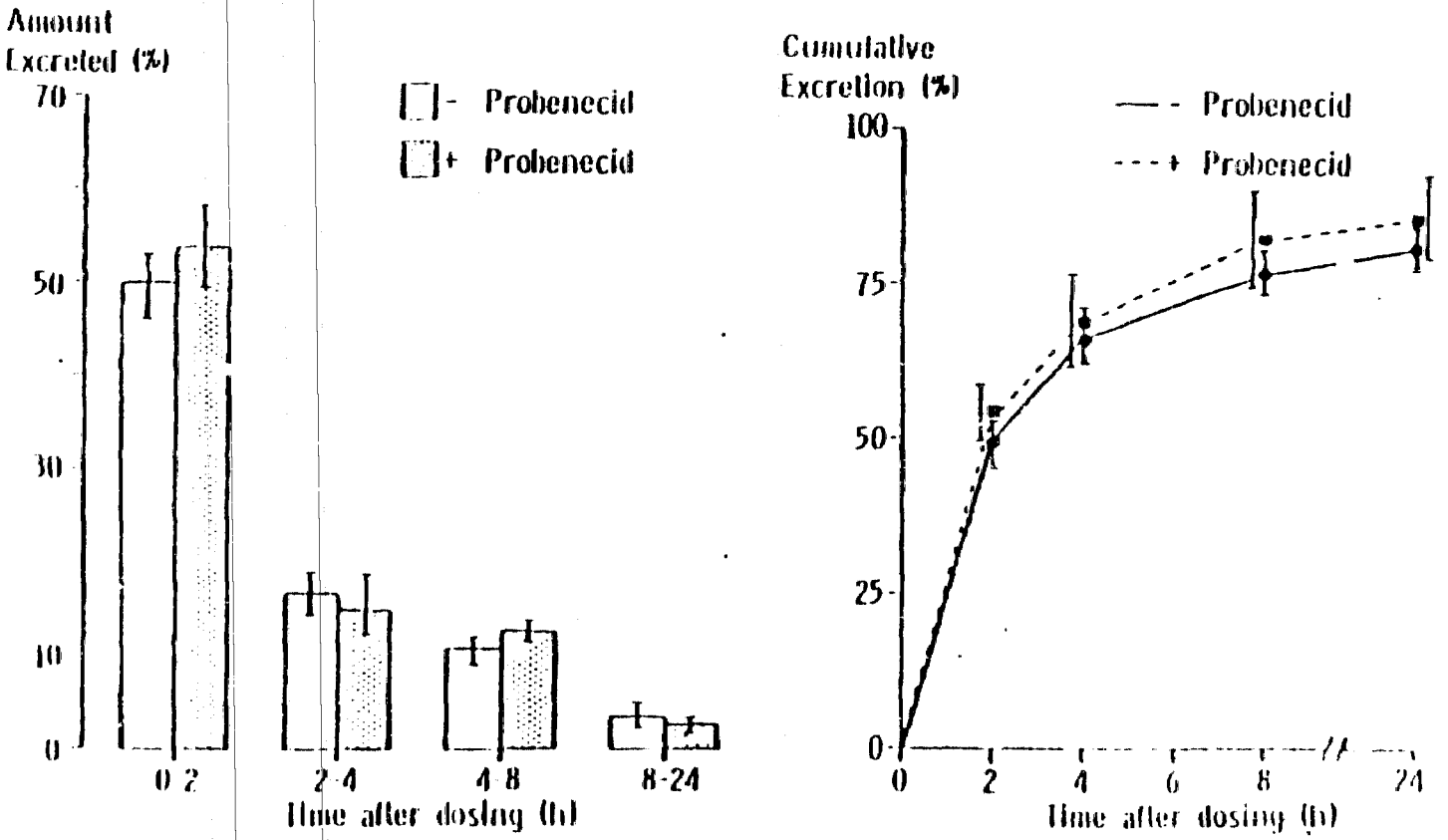


Fig 7

FIGURE 1

Serum level/time curve for ceftazidime after an intravenous infusion of 500mg ceftazidime over 30 mins to 6 male volunteers

mean ± 1 S.D.

(MIBA)

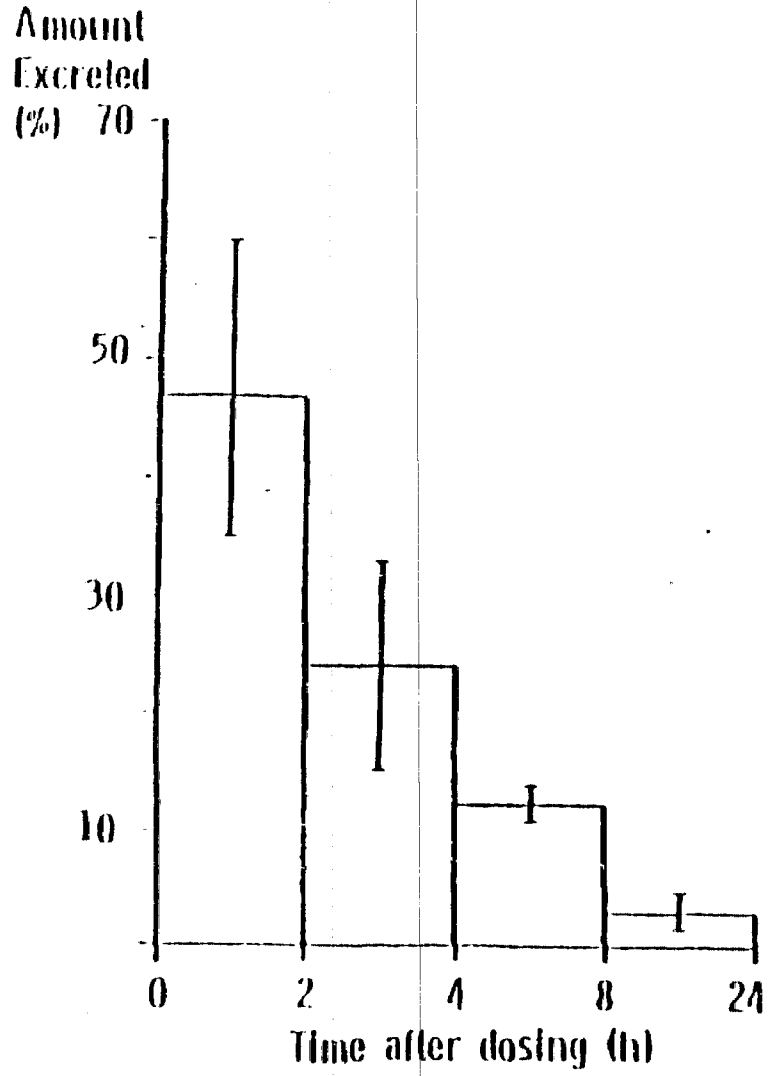
223 024

Fig. 2

Figure 1

FIGURE 2

Urinary excretion of ceftazidime after a 30 min intravenous infusion of 500mg ceftazidime to 6 male volunteers (MBA)



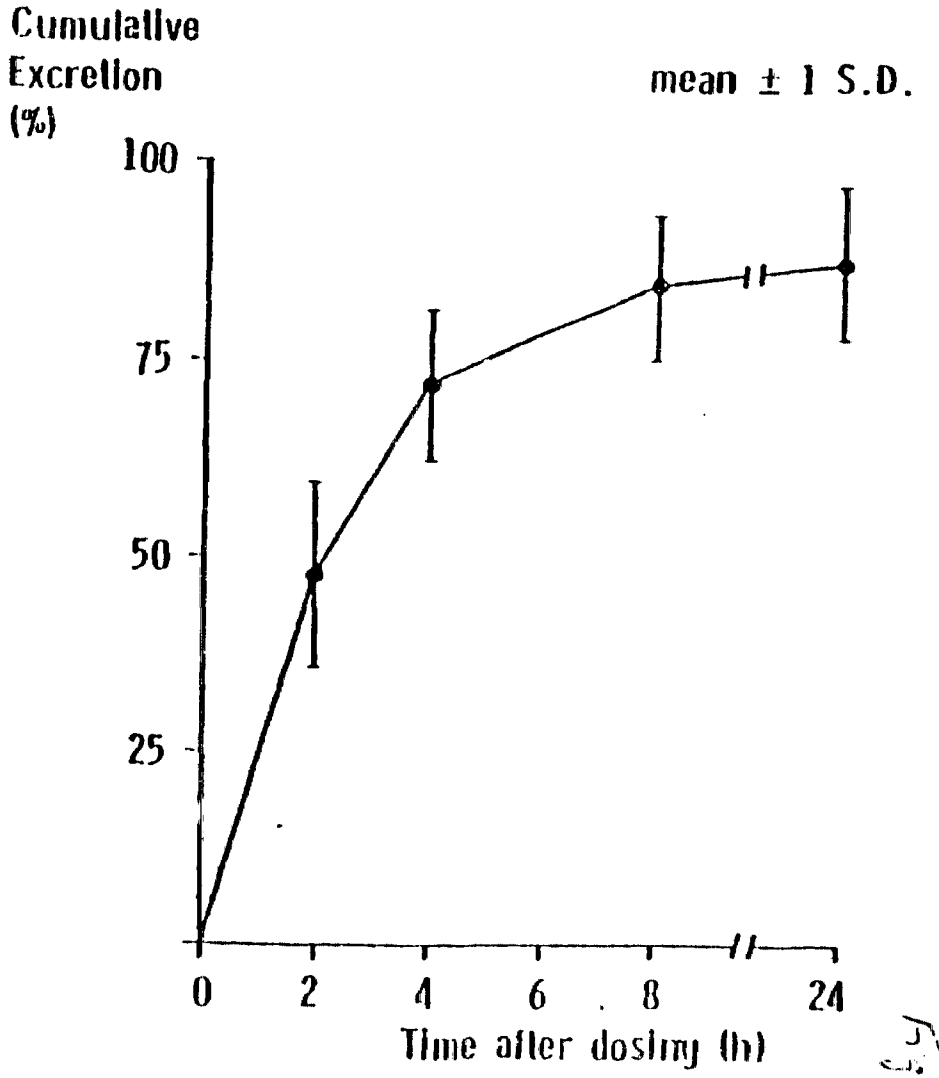
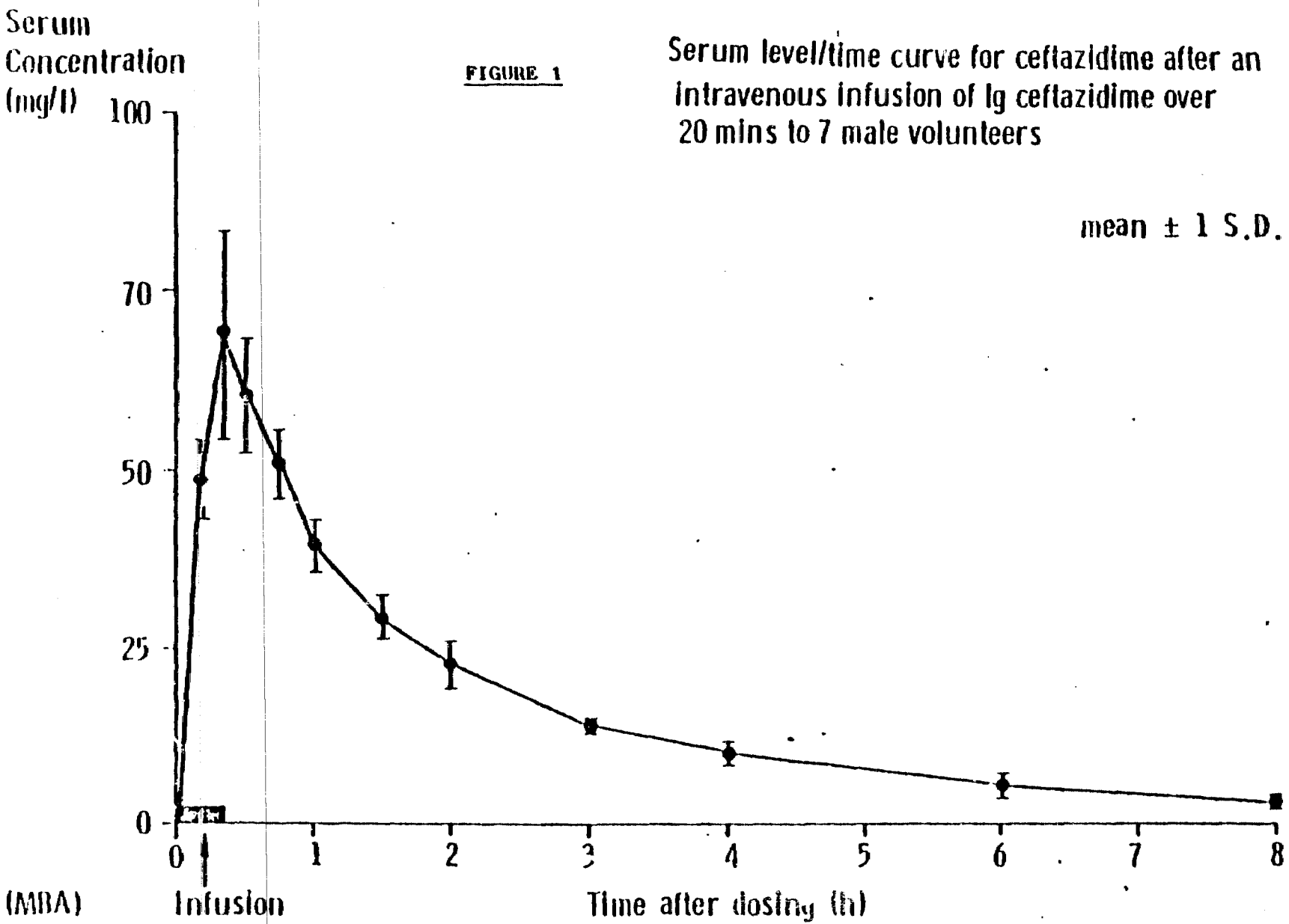


FIGURE 1

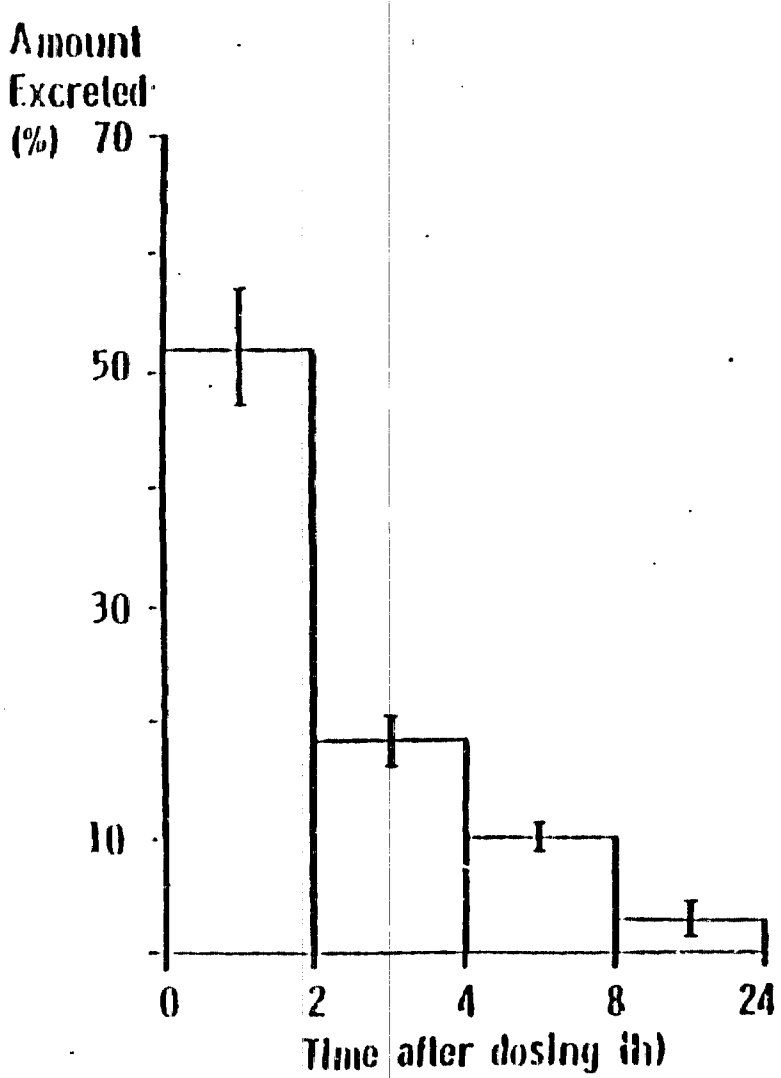
Serum level/time curve for ceftazidime after an intravenous infusion of 1g ceftazidime over 20 mins to 7 male volunteers



(MBA)

FIGURE 3

Urinary excretion of ceftazidime after a 20 min intravenous infusion of 1g ceftazidime to 7 male volunteers (MBA)



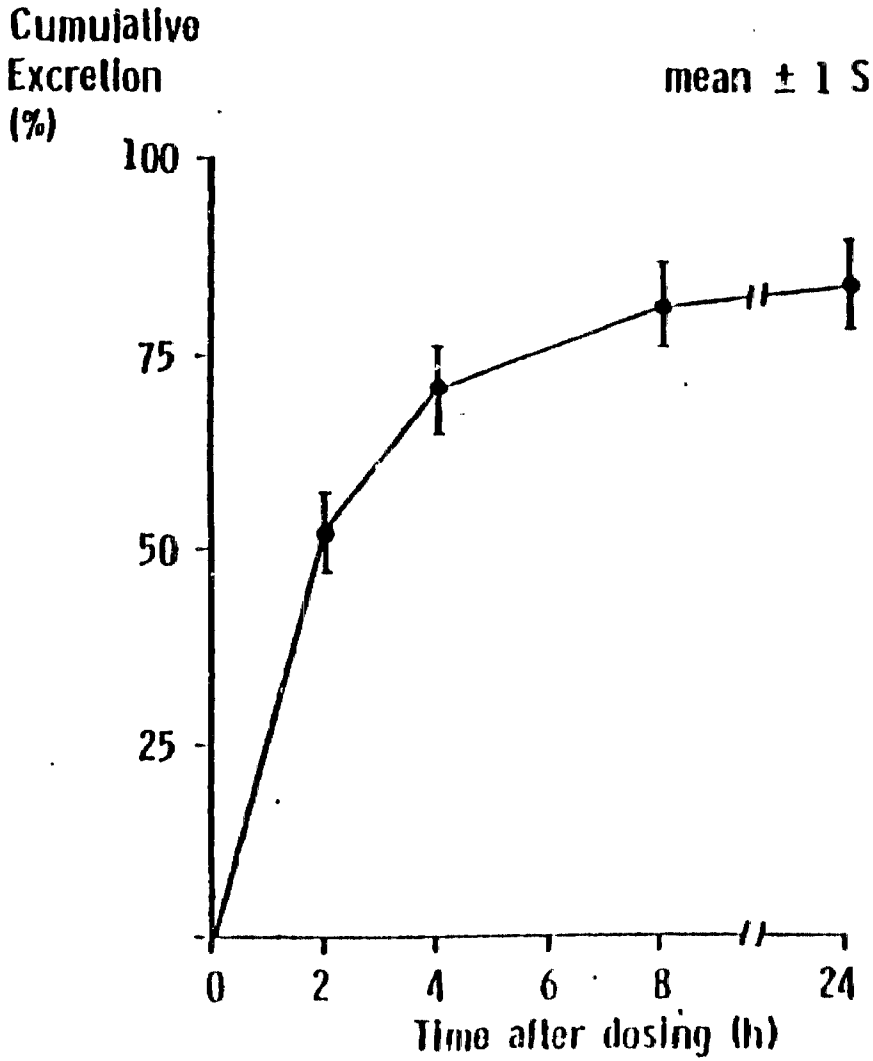
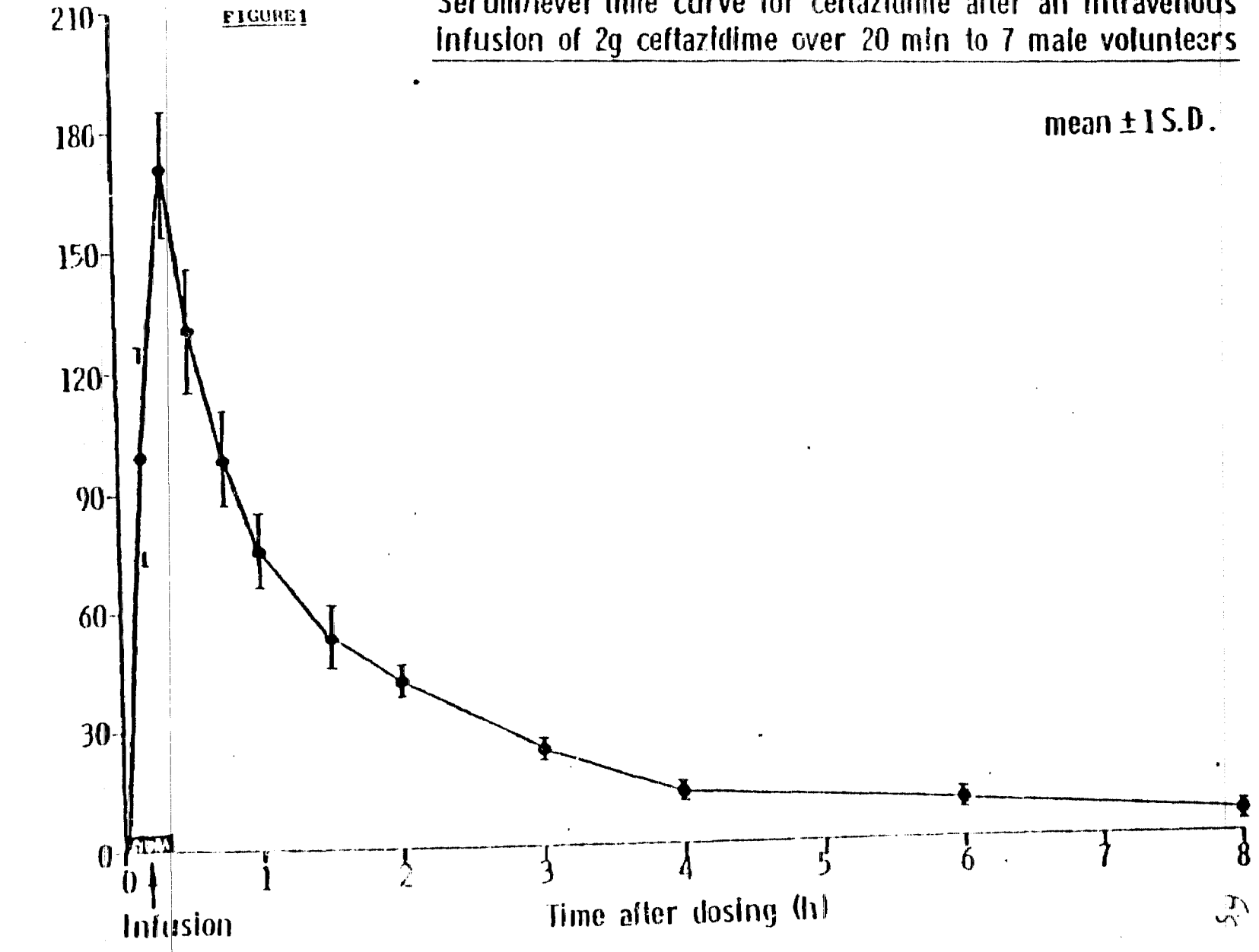


FIGURE 1

Serum/level time curve for ceftazidime after an intravenous infusion of 2g ceftazidime over 20 min to 7 male volunteers



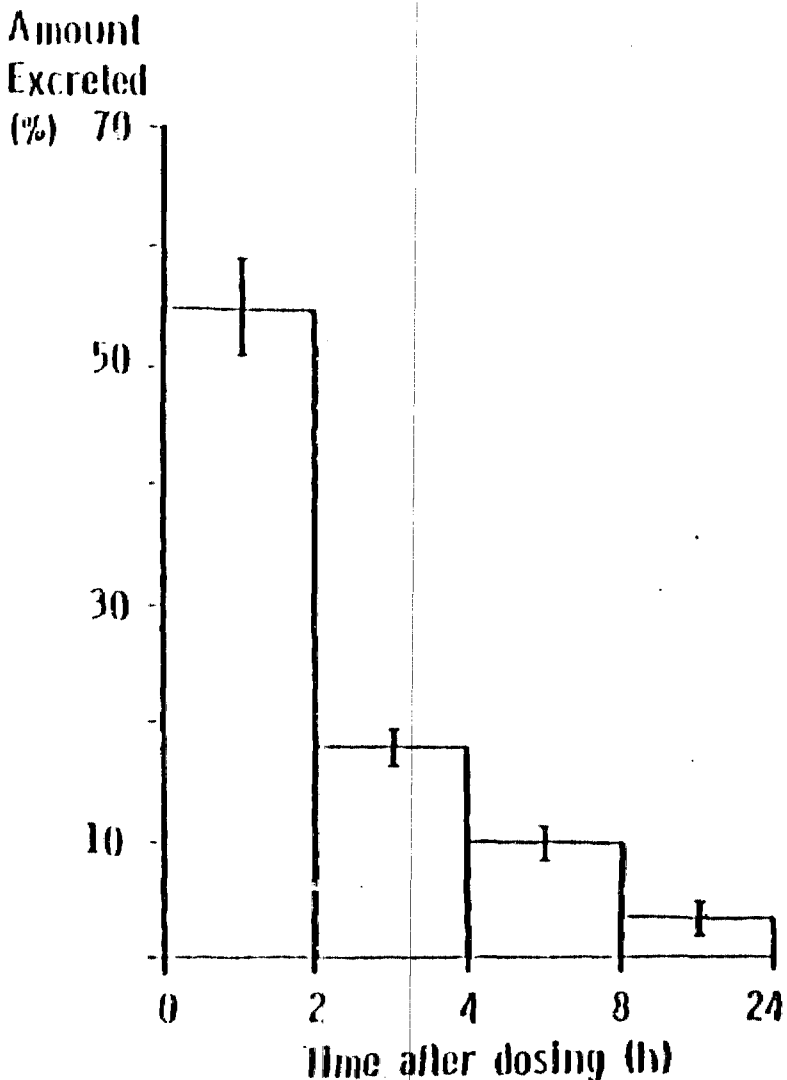
mean ± 1 S.D.

(MBA)

223 030

FIGURE 2

Urinary excretion of ceftazidime after a 20 min intravenous infusion of 2g ceftazidime to 7 male volunteers (MBA)



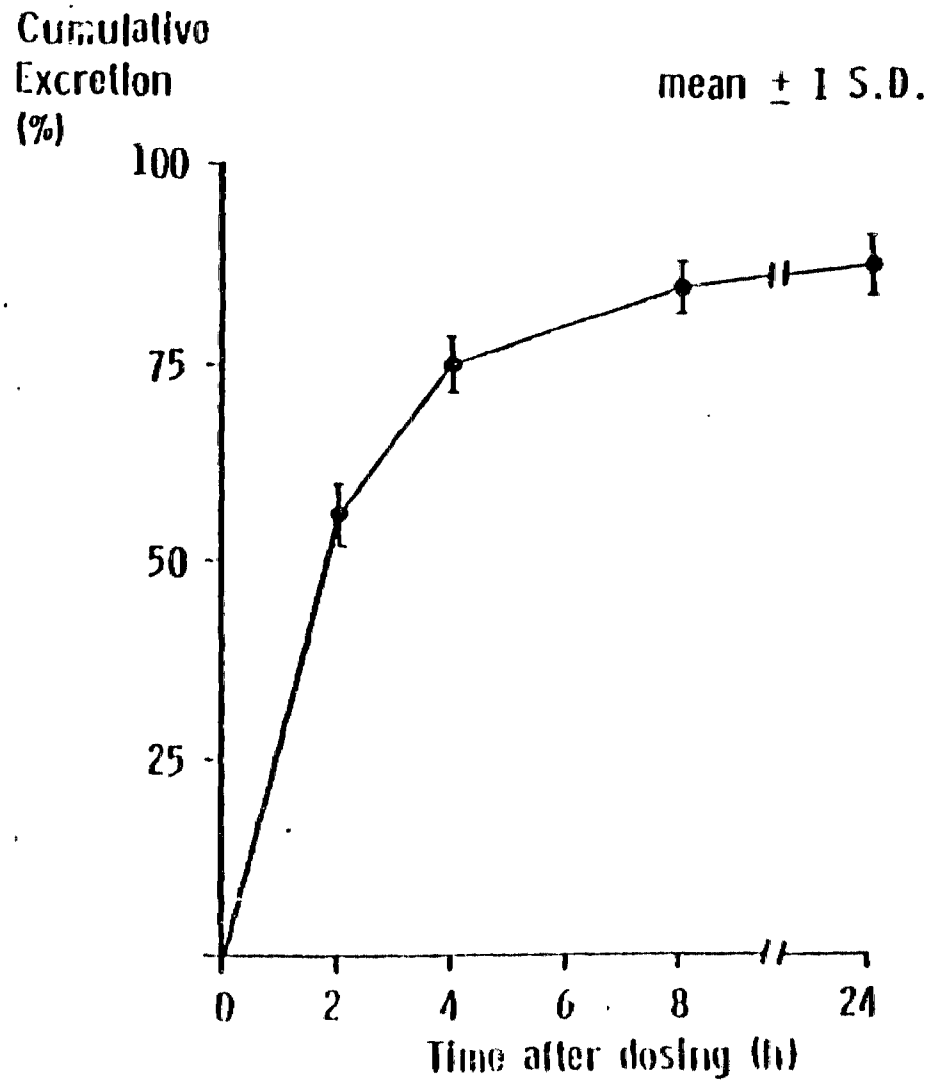
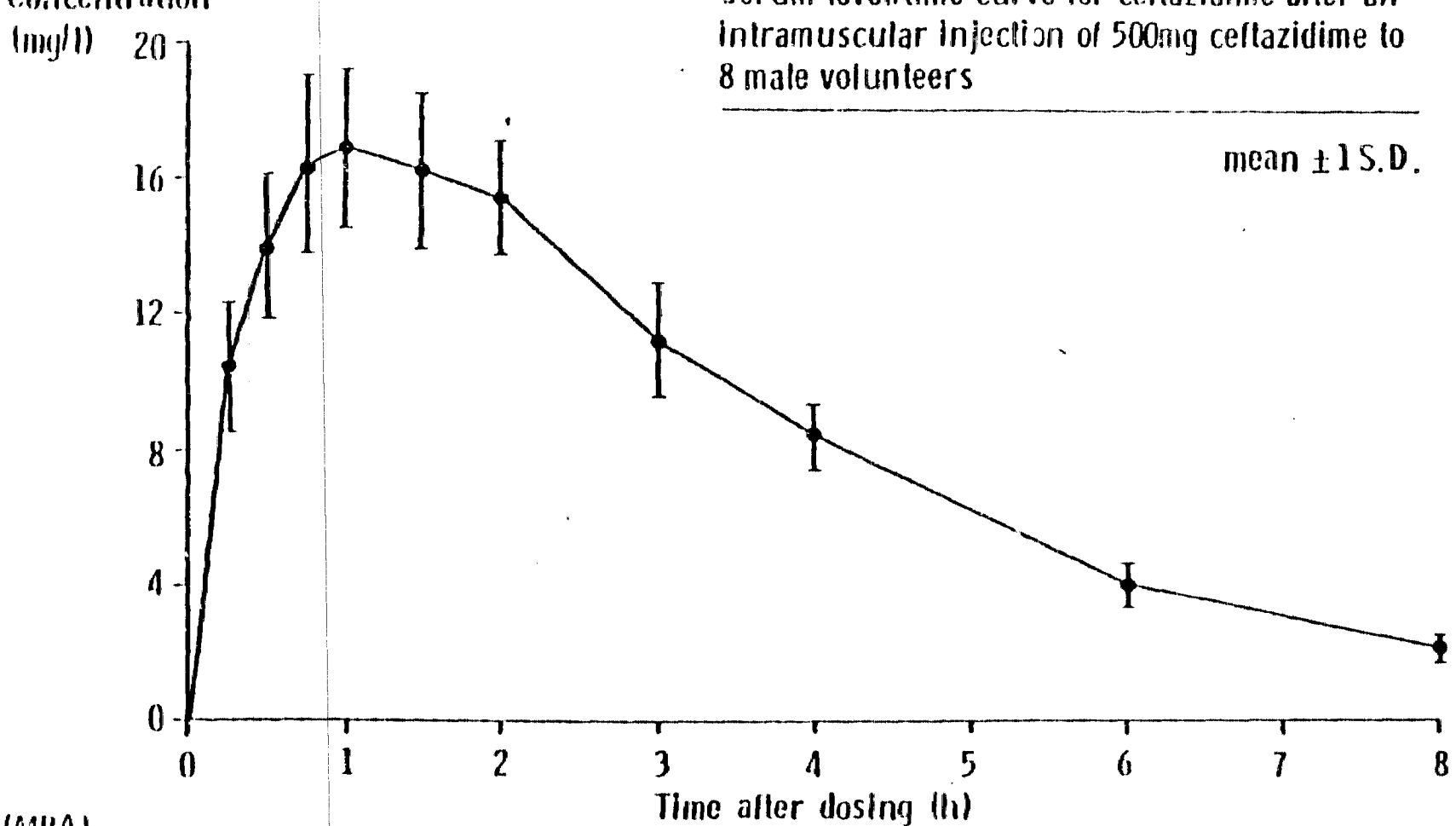


FIGURE 1

Serum level/time curve for ceftazidime after an intramuscular injection of 500mg ceftazidime to 8 male volunteers

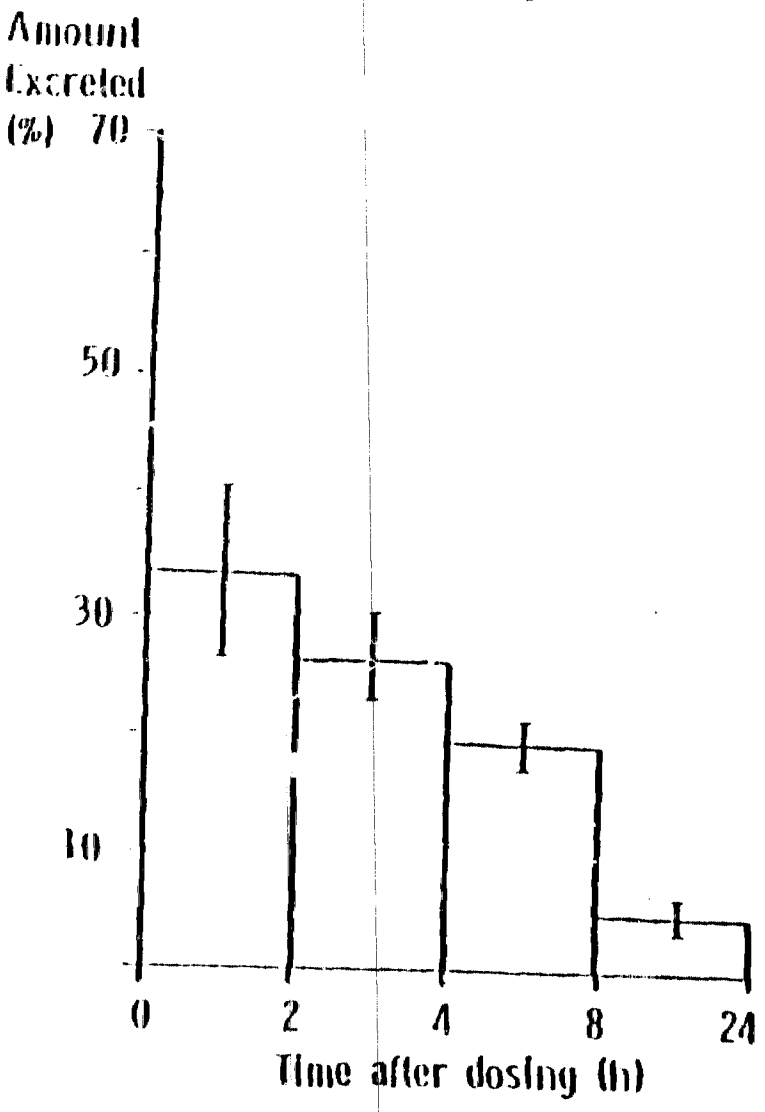
mean ± 1 S.D.



(MBA)

FIGURE 2

Urinary excretion of ceftazidime after an intramuscular injection of 500mg ceftazidime to 8 male volunteers (MBA)



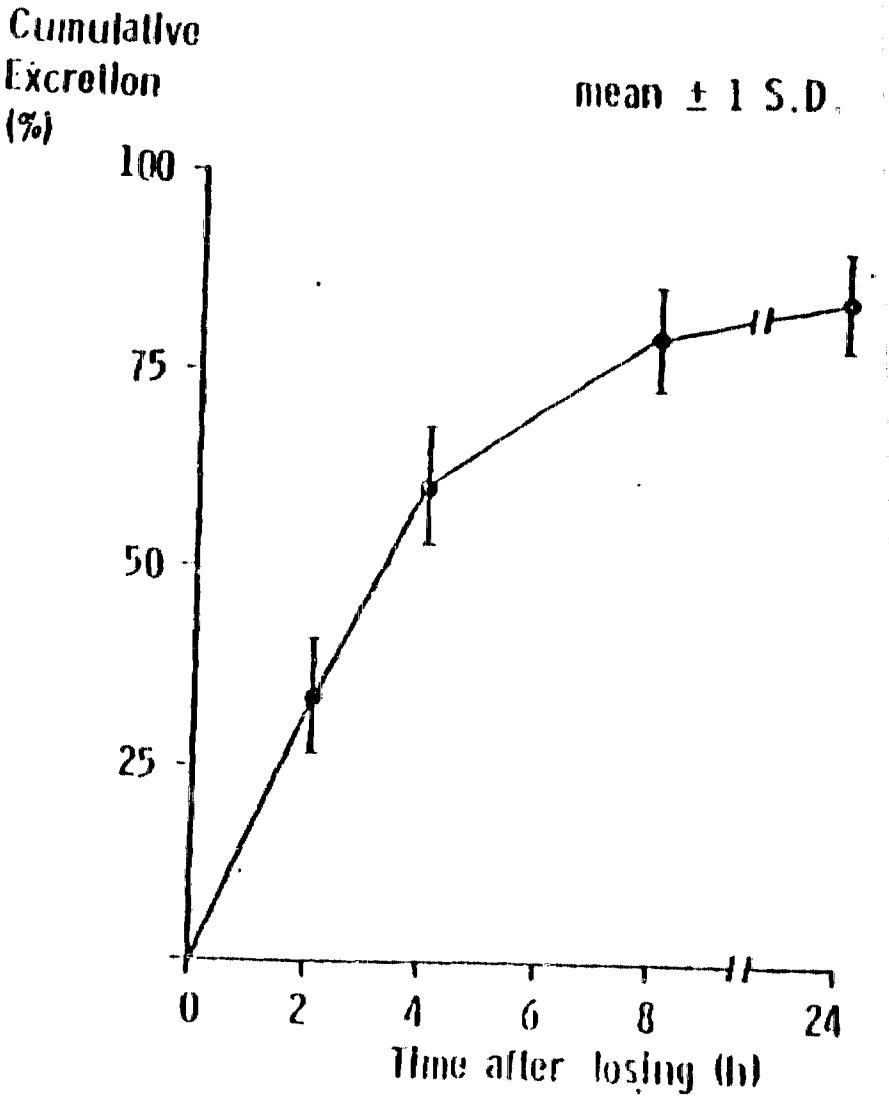
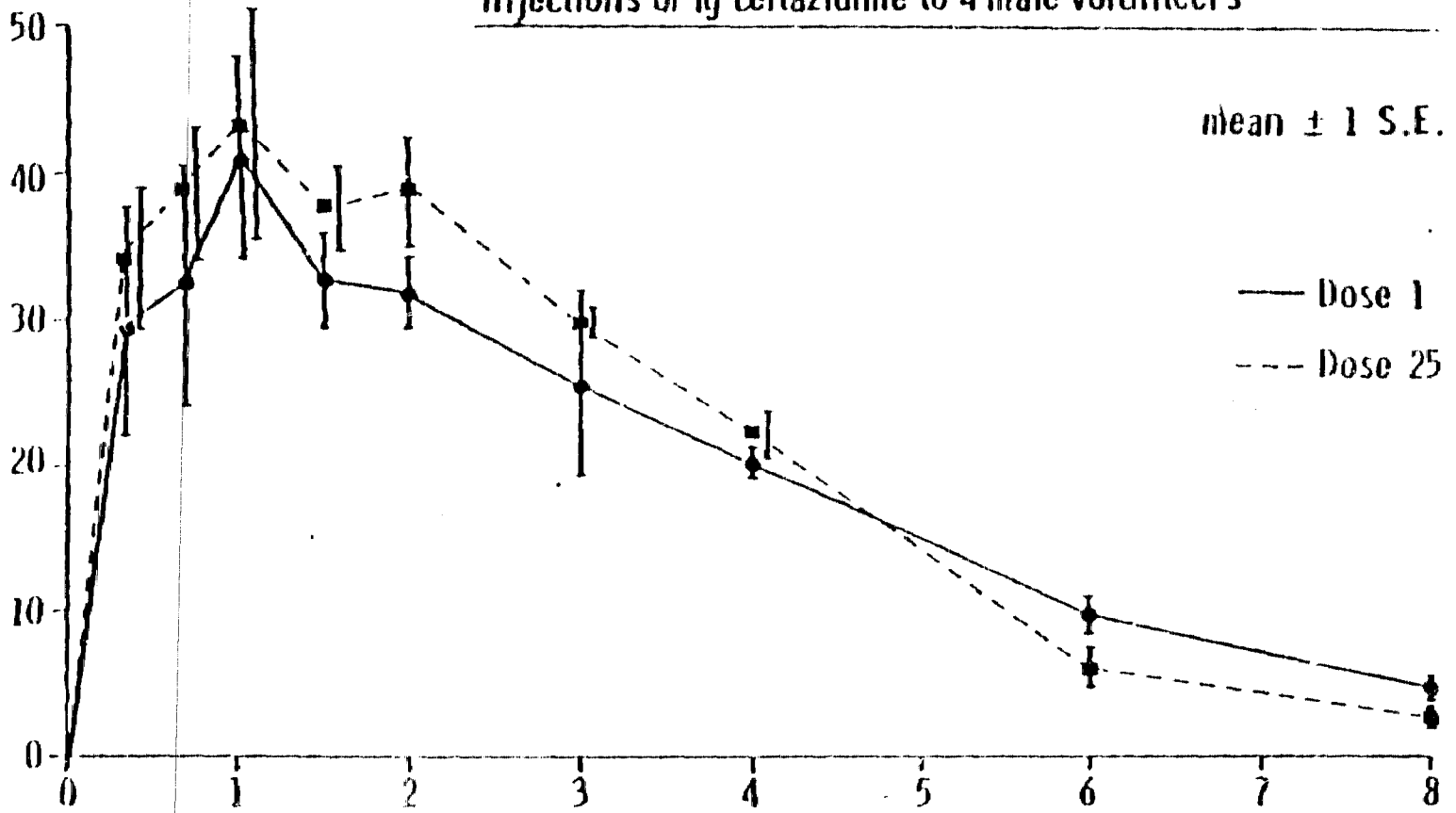


FIGURE 1

Serum level/time curves for ceftazidime after intramuscular injections of 1g ceftazidime to 4 male volunteers



(MBA)

Fig. 1 Average serum level/time curves after an intravenous injection of 2 g ceftazidime to 8 male volunteers

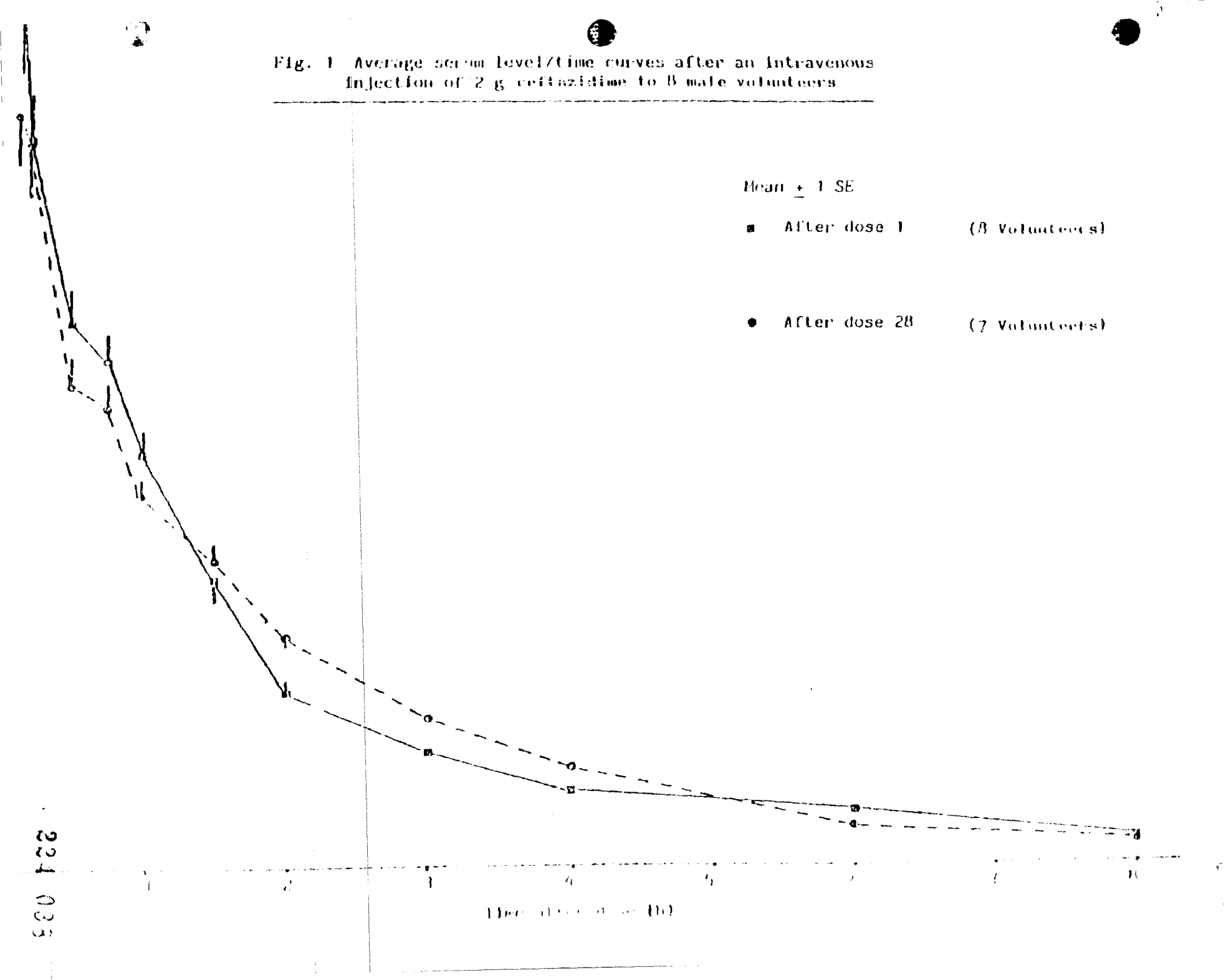
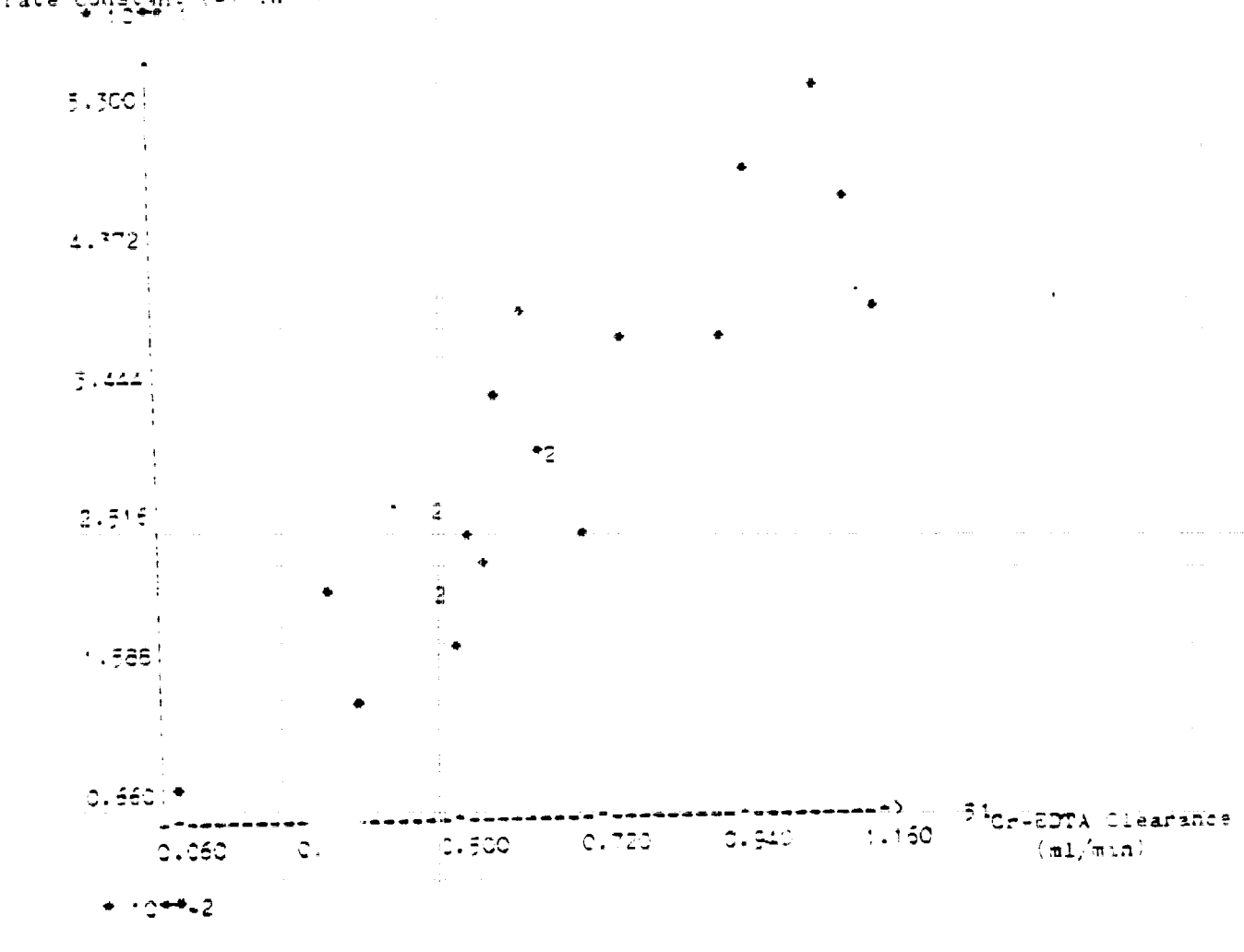


Figure 3 The relationship between serum elimination rate constant (β) and ^{51}Cr-EDTA clearance (GFR)



number of points = 23

23 PAIRS

CORRELATION COEFFICIENT = 0.8919
UPPER LIMIT= 0.9536 LOWER LIMIT = 0.7587

REGRESSION LINE -- Y=A+BX
A= 0.044068 B= 0.003776

MEAN= 65.86957 YMAP= 0.288400

Fig 7

Figure 4 The relationship between serum elimination half life and glomerular filtration rate

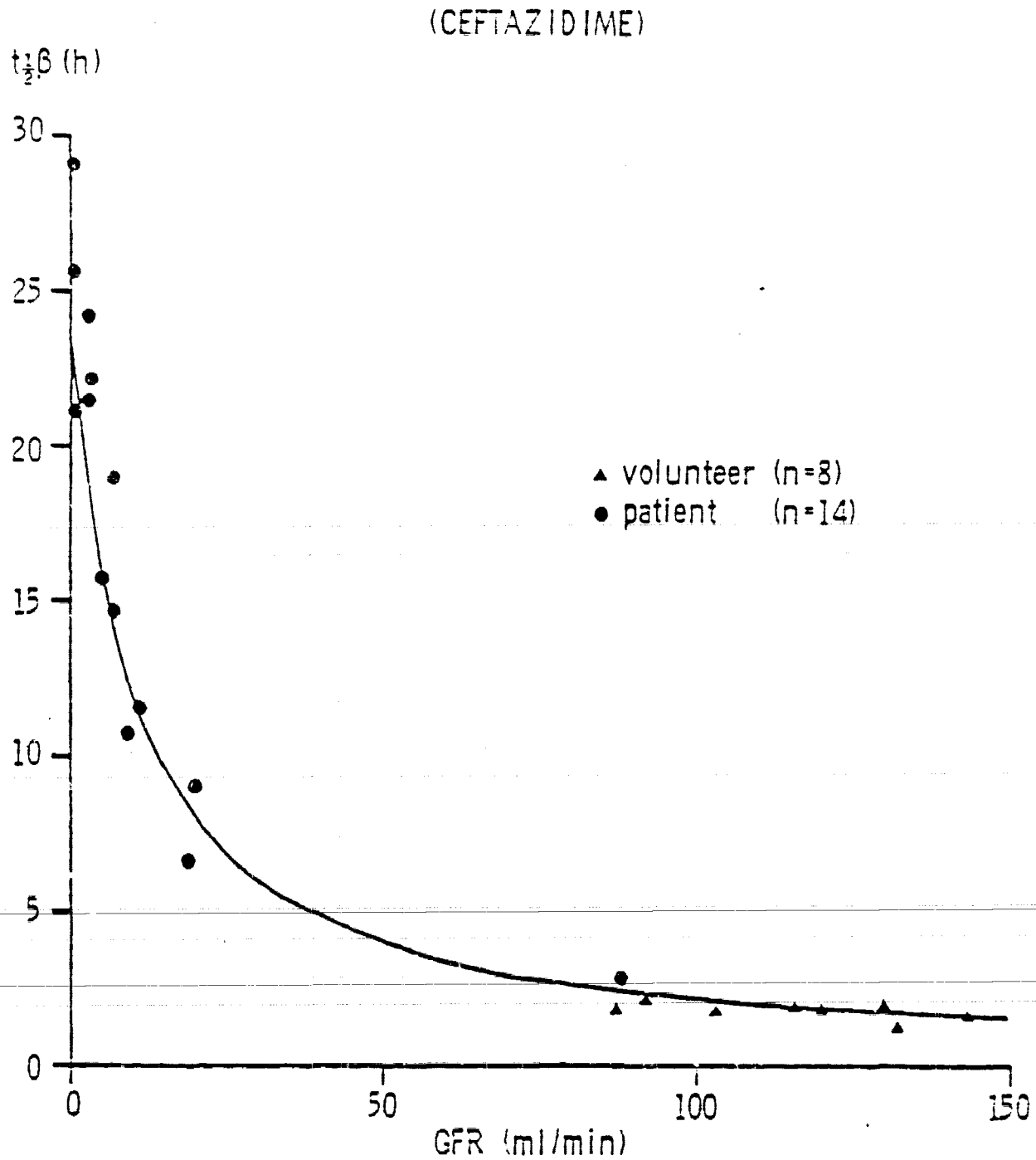
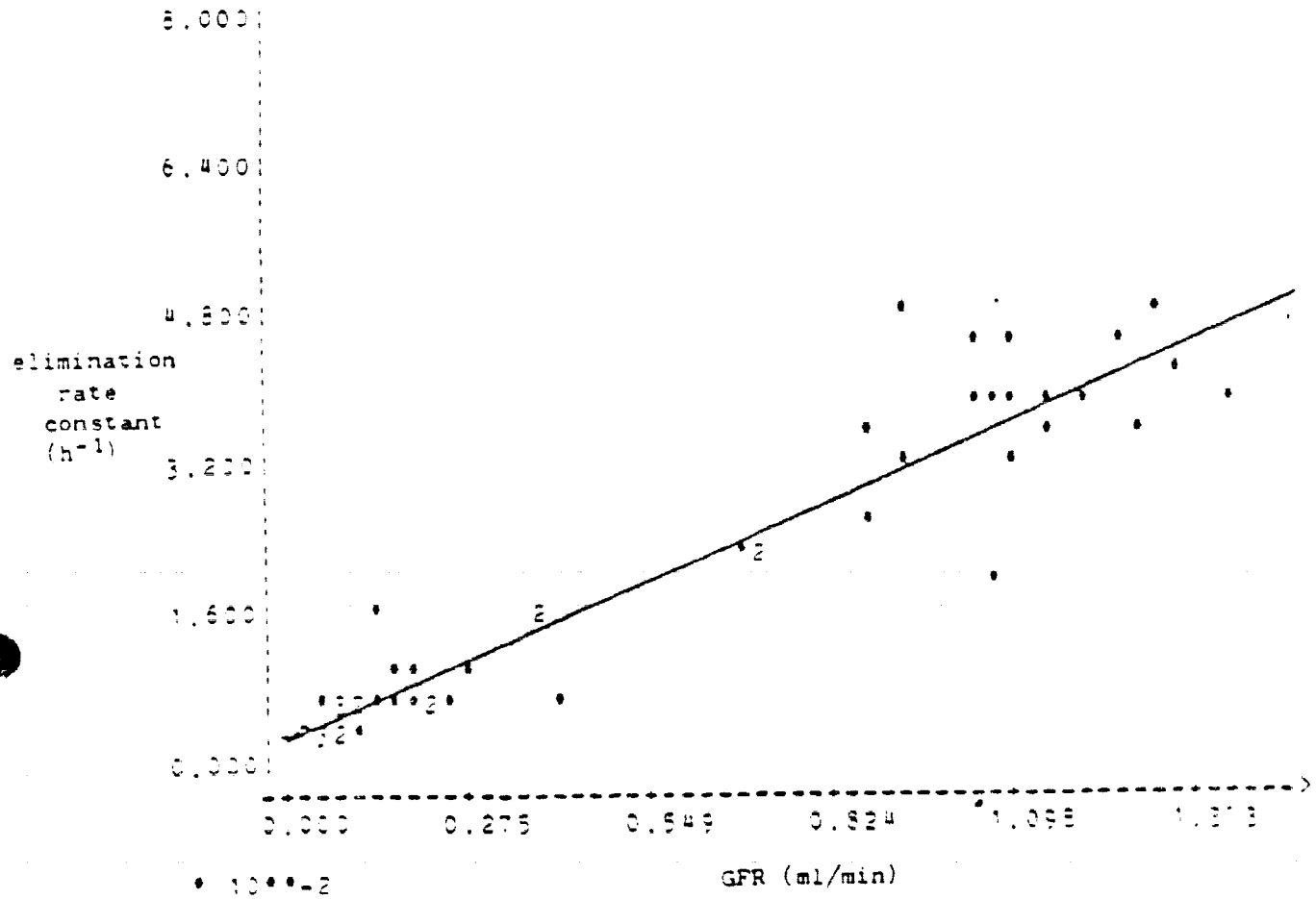


Figure 6 The relationship between serum elimination rate constant and glomerular filtration rate (Gower et al, Hoeffler et al, Olier et al)



Number of points = 68

68 PAIRS

CORRELATION COEFFICIENT = 0.9622
UPPER LIMIT= 0.9766 LOWER LIMIT = 0.9393

REGRESSION LINE -- Y=A+BX :
A= 0.028665 B= 2.903304

XBAR= 40.78162 YBAR= 0.155265

Fig 1

Figure 9 The relationship between predicted trough serum level and glomerular filtration rate after 1g ceftazidime intravenously

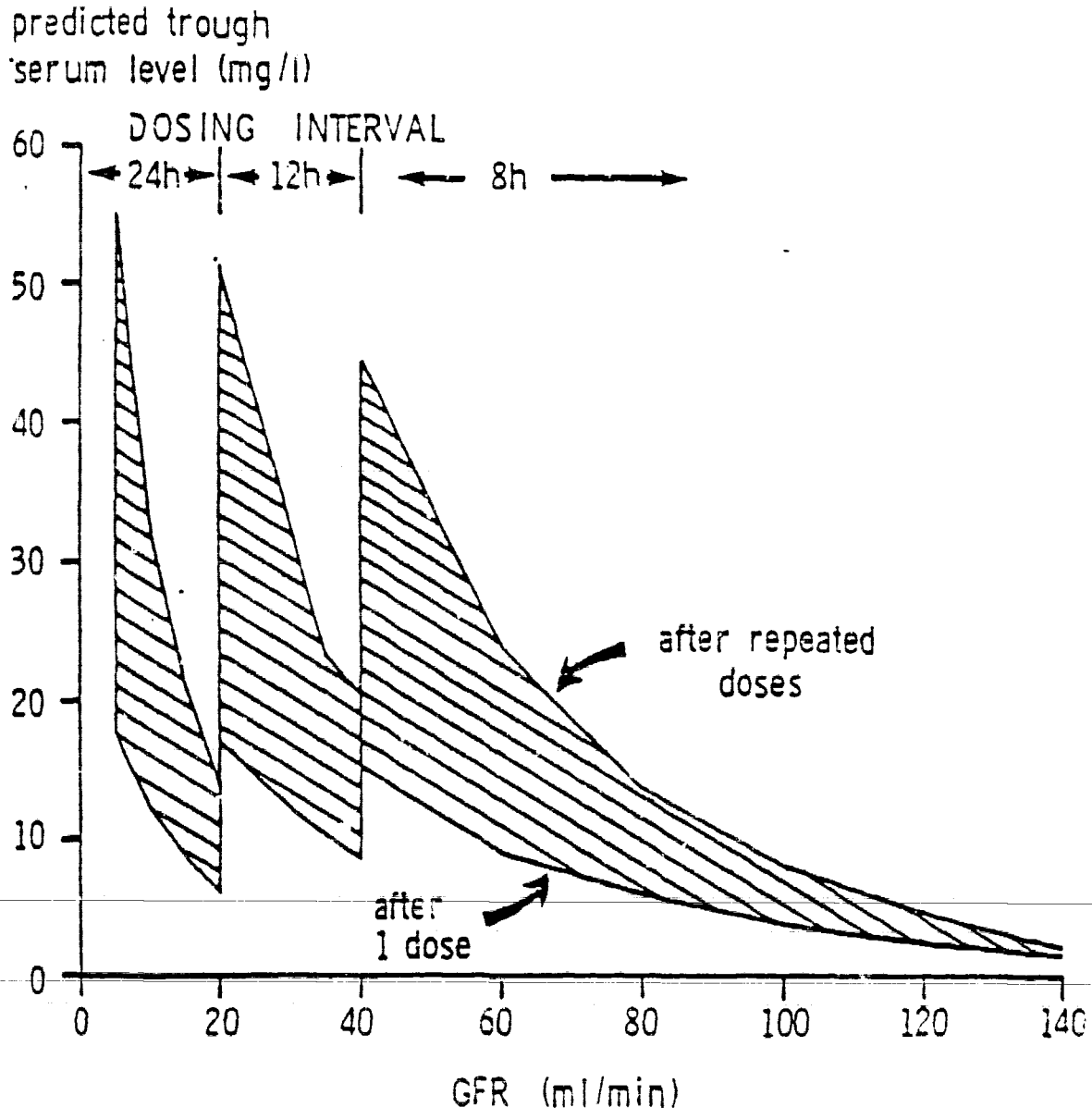
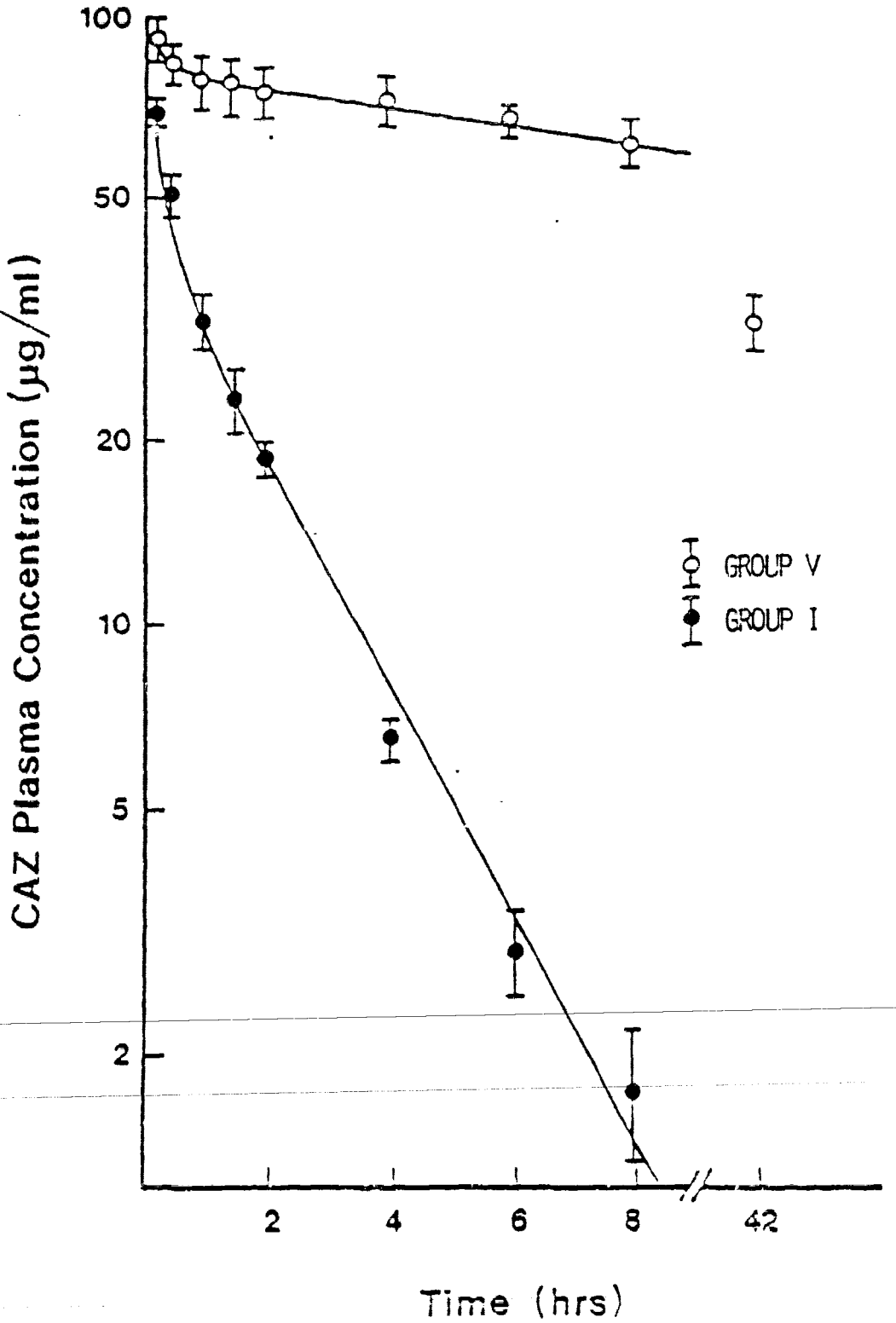
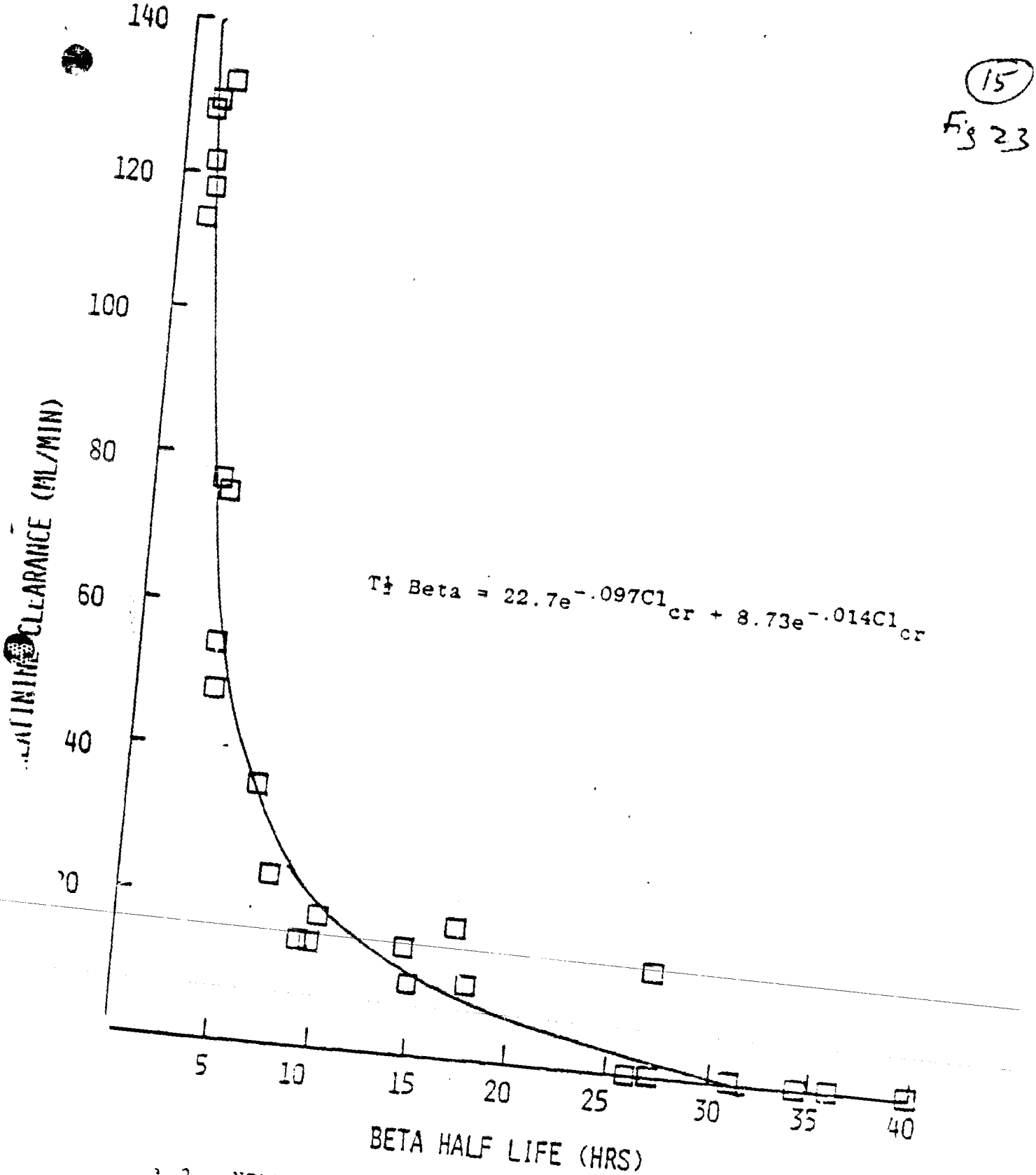


Figure I


100
50
20
10
5
2
CAZ Plasma Concentration (µg/ml)
GROUP V
GROUP I
2
4
6
8
42
Time (hrs)

(15)

Fig 23


140
120
100
80
60
40
20
CREATININE CLEARANCE (ML/MIN)
T½ Beta = 22.7e^-.097Cl_cr + 8.73e^-.014Cl_cr
5
10
15
20
25
30
35
40
BETA HALF LIFE (HRS)

CHEM. REVIEW

DRUG CONTROL REVIEW NOTES

Form 5 #50-578 Rx, Cephalosporin

DOSAGE FORM: ceftazidime for injection

SPONSOR: Glaxo, Inc.

3306 E. Chapel Hill-Nelson Hwy., Research Triangle Park, NC 27709

SUBMISSION REVIEWED:

a. Original dated: May 23, 1983

b. Amendments dated:

c. Providing for:

NAMES:

a. TRADE: Fortaz

b. NON-PROPRIETARY: ceftazidime for injection

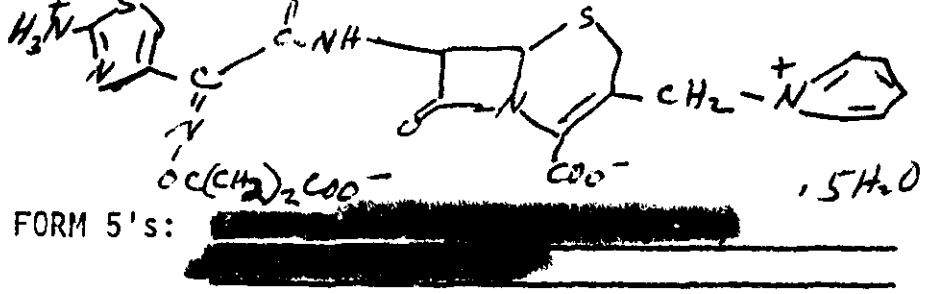
c. CHEMICAL: (6R, 7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-carboxyprop-2-yloxyimino)acetamido]-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylate pentahydrate.

d. ESTAB: none designated.

e. USAN: ceftazidime

f. WHO:

STRUCTURAL FORMULA:



RELATED NDA, IND, MF, FORM 5's: [redacted]

CONCLUSIONS: The manufacuring and controls are pending agreement on the drug monograph.

(Reviewer) James R. King 9/9/83

James R. King
2/20/85

cc: Form 5
Orig.
DUP/HFN-235
TRIP
HFN-815
HFN-815/CSO
HFN-178
HFN-815/RNorton
HFN-315/JRKing/10/18/84/12/7/84
R/D init. by: RNorton

MEMOS

Antibiotic Form 5 # 50-678

Memorandum of Meeting
held on November 27, 1984

Between

Glaxo

M. David MacFarlane, Glaxo, Inc.
Peter J. Wise, Glaxo, Inc.
John M. Padfield, Glaxo, Inc.
Desmond Poynter, Glaxo, Inc.
Ken Lees, Glaxo, Inc.
Jack Jefferies, Glaxo, Inc.

and

FDA

John M. Davitt
James R. King, Ph.D.
John D. Harrison (HFN-235)
Gamil Debbas, Ph.D.
T. Greene Reed, M.D.
Richard Norton
Albert T. Sheldon

Subject: Ceftazidime

We met to discuss the need for the test for high molecular weight polymer (HMWP) in the ceftazidime monograph.

Mr. Norton explained that the Eli Lilly & Co. was recommending that such a test be added to the ceftazidime monograph. Due to toxicity of the polymer and the potential development or increasing amounts of HMWP during storage.

Dr. Lees explained that Glaxo has now made about sixty batches and can meet a limit of no more than 0.12% HMWP at a time of manufacture and 0.4% throughout the expiry.

Dr. Debbas asked at what level does it cause toxicity and is it species specific.

Dr. Poynter described their toxicity studies showing that ceftazidime free of HMWP is quite safe.

Mr. [illegible] developed [illegible] use of trifluoro acetic [illegible] phase [illegible] pH 3, gradient 100; acetonitrile [illegible] and [illegible] meter with an assignment of purity [illegible] in terms of polymer greater than [illegible] difficulties with the packing for [illegible] separate production batches of the same [illegible] results varied by factors as high as 1.5 due to large part to influence of low molecular weight polymers that separate with difficulty. It was mentioned that the packing exclusion limits were: protein, 10,000, dextrans, 7,000 and polyethylene glycol 3,000. The manufacturer uses PEG 3000 for standardization with limits of + 30%.

We discussed the monograph as follows: Glaxo representatives did not want to hold up approval of the NDA because all assays in the monograph were not complete. They could agree to an interim monograph not containing methods for HMWP. They also presented evidence that there is a relationship between formation of pyridine in the product and development of additional HMWP after manufacture. They proposed to maintain the test for HMWP as a release specification for new batches and to control development of HMWP after manufacture by keeping the pyridine limit below 0.4% for the shelf life of the product. The .4% limit would only be for dry [illegible] and all injections into chromatographic equipment for assay would [illegible] be done immediately after reconstitution.

To determine the [illegible] they proposed the following:

dry the sample for 4 hrs. at [illegible] and then [illegible] water of crystallization. Further dry the same sample at 1000 C for 3 hrs. to remove the water and CO_2 from the sodium salt and then measure the loss gravimetrically. Determine sodium content by atomic absorption, calculate the sodium carbonate from the sodium content and calculate the bicarbonate water and carbon dioxide from the weight loss of the ceftazidime bicarbonate blend. Use these figures in correcting the assay for ceftazidime potency on a microgram per milligram basis.

We gave them a draft monograph. The Glaxo officials agreed to further study the problem with the chromatographic packaging material and to supply a detailed description of the pyridine and bicarbonate assays.

Richard Norton

cc: Orig. Form 5 # 50-578
HFN-315/CSO
HFN-815/[illegible]/82
HFN-815 [illegible]

Memorandum of Telephone Conversation
held on February 28, 1985

Between

James R. King, HFN-815

and

Mr. Paul [illegible]

Subject: [illegible] package insert [illegible] shelf life.

Mr. Ossi called to point out that recent drafts of the package insert included a statement of shelf life in the frozen state of 6 months, while the data only provide for 3 months, which was initially requested in the draft package insert. I told Mr. Ossi that I could only grant 3 months shelf life in the frozen state of 6 months, while the data only provide for 3 months, which was initially requested in the draft package insert. I told Mr. Ossi that I could only grant 3 months shelf life with that amount of data. Mr. Ossi agreed and acknowledged Glaxo's error. He also agreed to change the package insert to provide for 3 months frozen storage instead of the 6 months inadvertantly included in recent drafts of the package insert.

James R. King 3/1/85
/James R. King
3/27/85

cc: Orig. Form 5 #50-578
HFN-815
HFN-815/CSO
HFN-178, HFN-235
HFN-815/JRKing/3/1/85/dv

Antibiotic Form 30-578

MEMORANDUM OF TELEPHONE CONVERSATIONS

Between: James M. Chubb, Ph. D.
Associate Director of Clinical Research (919-248-2184)
or
M. David MacFarlane, Ph.D.
Director of Regulatory Affairs (919-248-2100)
Glaxo, Inc.

and

Theresa Greene Reed, M.D.
Medical Officer, HFN-815

Subject: Ceftazidime proposed labeling

January 18, 1985 I called Dr. Chubb to tell him that I am being challenged about recommending some of the micro-organisms in the proposed labeling. Some of them for which there are very few cases may have to be deleted and a revised copy of the proposed labeling will be needed. I won't know which ones must be deleted until we have had a chance to discuss this problem in-house. We discussed the total numbers for some of the pathogens which are being questioned.

January 28, 1985 I called Dr. MacFarlane to tell him that I had just been notified by the Group Leader that we will need a safety update before a letter can be issued for the application. He put Dr. Chubb on the line for a conference call. I described the format for a safety update that had been filed for another Form 5. Dr. MacFarlane replied that they will start on this immediately.

I asked Dr. Chubb to add an appropriate sentence to give the duration of treatment and I gave him several examples.

January 29, 1985 I called Dr. Chubb to tell him that while preparing the Summary Basis of Approval I noticed that two of the largest bone and joint infections studies had not been included in the overall summary table. I am amending my MOR to include these cases which were left out. I asked him to file a revised summary table so that the table in the original application will not be misleading to the reader.

January 31, 1985 Dr. MacFarlane called to tell me that they have several changes to make in the proposed labeling. Dr. Chubb will give them to me.

January 31, 1985 I called Dr. Chubb to tell him that members of the review team in the Division had just met to consider the individual micro-organisms for each claim. I gave him the recommendations which are given in my amendment to my MOR dated Jan. 18 and 31, 1985. Dr. Chubb accepted the fact that some would have to be deleted since we had already discussed the number of cases that supported these claims. He replied that he will probably be asked to check newly generated data to see if any of these organisms can be retained. Approximately 10,000 cases have been treated, way beyond the 2648 in the application. When he asked if this new data should be filed, I replied

that it would mean more time for another detailed review. There is agreement now within the Division about the microorganisms and the package should move forward without delay. More cases would delay it. Dr. Chubb replied that they will prepare revised labeling.

Dr. Chubb gave me the following labeling changes that Glaxo wants to make:

1. The pH range should be 5.0 to 8.0. This conforms with the monograph.

2. The sentence regarding monitoring is revised to read, "Further dosing should be determined by therapeutic monitoring, severity of the infection and susceptibility of the causative organism." No one has been able to support recommending that a trough level of 40 mcg/ml should not be exceeded.

3. In response to my request, the paragraph which follows will be added just before the Administration subheading, "NOTE: FORTAZ should be continued for two days after signs and symptoms of the infection have disappeared, but, in complicated infections, longer therapy may be required."

4. The dose for pseudomonal lung infections in patients with cystic fibrosis with normal renal function should be 30 to 50 mg/kg instead of 30 to 50 mg/kg. This was a typing error.

These changes are satisfactory.

I told Dr. Chubb that the overall age/sex summary table did not include patients in the two meningitis amendments. The total number of ceftazidime-treated patients is 2648 instead of 2539. The total number of control-treated patients is 1051 instead of 1019. I gave him the new numbers I had calculated for each age class for males, for females, and for the total for both ceftazidime and for the control and I gave him the new mean ages that I had calculated for each of the six columns. Because of this the adverse reaction rates must be corrected. There were two more diarrheas, one rash, and one nausea and vomiting to make 221 adverse events instead of 218 and in 161 patients instead of 158. My new overall adverse reaction rate is 6.1% instead of 6.2%. I asked him to verify the rates that are given in the labeling for each type of reaction.

Dr. Chubb replied that in working on the safety update, he is finding that the biggest change will be in hypersensitivity reactions, yet it is not likely that the rate given originally will change.

Thomas [illegible] Reed

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