CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-679/S-002

MEDICAL REVIEW(S)

AUG 22 1997

Joint Clinical/Statistical Review of NDA 50,679/SE1-002

NDA#:	50,679/SE1-002
Applicant:	Bristol-Myers-Squibb Pharmaceutical Research Institute
Name of Drug:	Maxipime® (cefepime) for injection
Indication:	Empiric therapy of febrile neutropenia
Type of review:	Clinical/statistical
Medical Officer:	David Ross, M.D., Ph.D.
Statistical Reviewer:	Alaka Chakravarty, Ph.D.

1 RESUME

Background: There are currently no antibiotics specifically approved for empiric therapy of febrile neutropenia. The first application for this indication, a supplement to NDA 50,679, has been submitted to the Food and Drug Administration by Bristol-Myers Squibb. The sponsor is requesting approval to label and market Maxipime® (cefepime HCl) for empiric therapy of febrile neutropenic patients.

Methods: Patient evaluability and outcomes in this supplement were assessed by an FDA medical officer in a blinded fashion. Efficacy analyses were performed from multiple perspectives by varying the definition of success while keeping the size of the evaluable population constant, using a primary set of evaluability criteria, as well as a modified intent-to-treat (MITT) approach.

Studies reviewed: Nine clinical studies were submitted in this NDA; 3 compared cefepime and ceftazidime monotherapy (647 patients, comprising 733 episodes); 2 compared cefepime to a ß-lactam/aminoglycoside combination (187 patients comprising 187 episodes); 1 compared cefepime in combination with vancomycin to the corresponding ceftazidime combination (111 patients comprising 128 episodes); and 1 compared cefepime combined with amikacin to the corresponding ceftazidime combination (353 patients comprising 353 episodes). Although there is no approved comparator for this regimen, all of the comparator regimens employed are accepted clinically as appropriate empiric therapy for febrile neutropenia. Two non-comparative studies were also submitted. The monotherapy studies were generally designed according to guidelines published by the Infectious Diseases Society of America.

Study population characteristics: Patient characteristics in the controlled trials were balanced between treatment arms with respect to demographics, risk factors for infection, and types of infection, and included patients with hematologic and solid malignancies, patients with severe and/or prolonged neutropenia, patients with indwelling vascular catheters, and patients on antimicrobial prophylaxis. There were relatively few patients with hypotension at presentation or a history of bone marrow transplantation. Patients presenting in septic shock were excluded from these studies.

Efficacy analysis: The two largest monotherapy trials, which were both multi-center, randomized trials, were poolable on the basis of similar study designs and homogeneity of treatment effect. In the pooled population database, 317/639 (49.6%) of first episodes were evaluable for efficacy. Early modification and loss to follow-up were the most common reasons for unevaluability. The primary definition of clinical response was defervescence without modification and without occurrence of new febrile episodes or documented infection. Under this definition, the individual monotherapy studies did not establish therapeutic equivalence between cefepime and ceftazidime. However, pooling of these two studies resulted in clinical response rates for cefepime that were therapeutically equivalent to ceftazidime under both the primary and MITT analyses, although the response rate for cefepime was lower than that for ceftazidime under both analyses. The point estimate of the difference in response rates between cefepime and ceftazidime for the pooled analysis was -4.3% for the evaluable population. The difference in response rates for all episodes (including patients who were re-enrolled) was -6.2% for the evaluable population and -4.0% for the MITT population. A third, smaller monotherapy trial also showed equivalence between cefepime and ceftazidime. Response rates in this study were lower in both arms than in the other two monotherapy trials. The point estimate of the difference in response rates was +4.4% in favor of cefepime.

Use of alternative definitions of clinical response, varying in strictness from defervescence without modification of the original regimen to survival regardless of modification, resulted in dramatic changes in cefepime response rates, ranging from 35%-95% for the evaluable population and 21%-95% for the MITT analysis. For the pooled monotherapy studies, cefepime was therapeutically equivalent to ceftazidime for all definitions of clinical response. However, the response rate for cefepime was lower than that for ceftazidime under all analyses, with the point estimate of the difference in first episode response rates ranging from -4.3% (for the primary endpoint) to -3.4% for survival regardless of modification.

A subgroup analysis of the pooled monotherapy studies showed that response rates for cefepime were lower than those for ceftazidime for patients with the highest risk of having a severe bacterial infection (such as patients with an underlying hematologic malignancy, those with severe or prolonged neutropenia, those with a history of recent bone marrow transplantation, and those presenting with hypotension). Response rates for most of the other subgroups were also lower in the cefepime arm, except for patients with an underlying solid malignancy.

Microbiologic response for specific pathogens was similar between treatment arms in the pooled evaluable patient data set except for primary infections caused by *Escherichia coli*; there were more treatment failures for this organism in the cefepime arm. This difference was statistically significant under the primary analysis, which counted secondary infections unrelated to the initial episode as failures. The difference in response rates for *E. coli* infections was not statistically significant for other definitions of response. The most common reason for *E. coli* infection treatment failures included superinfection by a different, resistant organism; occurrence of fever without a microbi-

ologically or clinically documented source of infection; and resistance of the original isolate. There were no cases in which there was persistence of a susceptible isolate.

The trials comparing cefepime with combination therapy did not establish therapeutic equivalence between cefepime and the comparator arm. Both of these studies had relatively small numbers of evaluable patients and were therefore underpowered to demonstrate equivalence. In addition, one of these studies (AI411-118) had a point estimate of -13.5% for the difference in response rates between cefepime and combination therapy; the size of this point estimate for this single study suggests that cefepime may have been inferior to the comparator regimen.

The studies comparing cefepime in combination with vancomycin or amikacin to the corresponding ceftazidime combination also did not establish therapeutic equivalence. Both of these studies, which were carried out in Europe, had small numbers of evaluable patients, due to study conduct involving use of prophylactic parenteral antibiotics in many study subjects, as well as failure to follow a substantial number of subjects beyond the end of therapy. Both studies showed lower response rates for the cefepime-containing treatment arm than for the comparator regimen. One study had a large point estimate for the difference in response rates between treatment arms, at -13.0%, while the other had a point estimate of -6.4%. Statistical analyses of these data suggest that cefepime combination therapy was inferior to the comparator regimen in these studies.

Safety analysis: There were no significant differences between cefepime and comparator treatment arms with respect to overall mortality, mortality due to specific causes, clinical adverse events, or laboratory adverse events.

Conclusions: The three studies comparing cefepime monotherapy to ceftazidime monotherapy were adequate and well-controlled. The two largest monotherapy trials, when pooled, and the third monotherapy trial, demonstrated therapeutic equivalence between cefepime and comparator for empiric therapy of febrile neutropenia, supporting the conclusion that cefepime monotherapy is safe and effective for this indication. The studies involving combination therapy with cefepime were not adequate to demonstrate efficacy of the combination regimen.

Recommendations:

1. Approval of the claim of safety and effectiveness of cefepime monotherapy as empiric therapy for febrile neutropenia, with appropriate labeling to exclude use as monotherapy for patients at high risk for severe infection.
2. Non-approval of the claim of effectiveness of cefepime in combination as empiric therapy for febrile neutropenia.
3. A phase IV commitment to perform an adequate and well-controlled study examining the use of cefepime in combination with an aminoglycoside or vancomycin.

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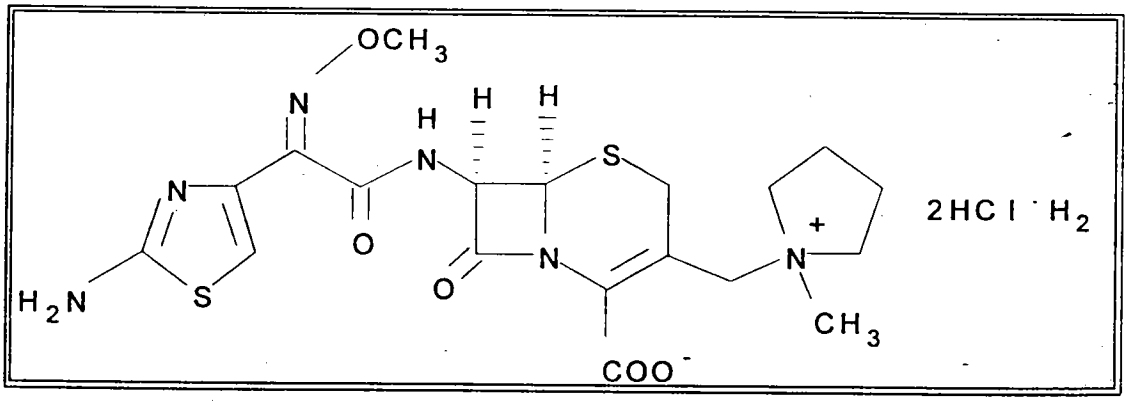
3 GENERAL INFORMATION

NDA number
50, 679/SE1-002

Applicant identification
Name: Bristol-Myers Squibb Pharmaceutical Research Institute
Address: 5 Research Parkway, P.O. Box 5100
Wallingford, CT 06492-7660

Submission/review dates
Date of submission: May 17, 1996
CDER stamp date: May 20, 1996
Date submission received by reviewer: May 21, 1996
Date review begun: June 3, 1996
Date review completed: June 12, 1997

Drug identification
Generic name: cefepime hydrochloride
Trade name: Maxipime®
Chemical name: 1-[[6*R*, 7*R*)-7-[2-(2-amino-4-thiazolyl) glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7^2-(*Z*)-(*O*-methyloxime), monohydrochloride, monohydrate
Chemical structure:



CAS registry number: 123171-59-5
Molecular formula: $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$
Molecular weight: 571.51

Pharmacologic category
Cephalosporin

Dosage form
Sterile powder for reconstitution

Route of Administration
Intravenous

Proposed Indication and Usage

Empiric therapy of febrile episodes in neutropenic patients. The applicant proposes the following labeling:

Proposed Dosage and Administration

Related drugs and submissions

IND
IND

Material Reviewed

SNDA volumes: The submission consists of 103 volumes, organized as follows:

Vol. 1	Overall summary
Vol. 2	References; WordPerfect 6.1 diskettes containing text of integrated summary of safety and efficacy and nine clinical study reports
Vols. 3-4	Comparative clinical study AI411-204
Vol. 5	Comparative clinical study AI411-189
Vol. 6	Comparative clinical study AI411-131
Vol. 7	Comparative clinical study AI411-137
Vol. 8	Comparative clinical study AI411-118
Vol. 9	Comparative clinical study AI411-186
Vol. 10	Comparative clinical study AI411-198
Vols. 11-15	Non-comparative clinical study AI411-143
Vol. 16	Non-comparative clinical study AI411-158
Vols. 17-64	Case report tabulations
Vols. 65-103	Case report forms

Other documents reviewed:

7/26/93	Anti-Infective Drug Products Advisory Committee (AIDPAC) meeting minutes
9/26/93	Presentation to AIDPAC by Linda Sherman, M.D.
1996	Periodic Adverse Drug Experience Reports
1996	Annual Report for IND
3/5/97	AIDPAC meeting minutes

1 Material in parentheses presented as a footnote in the proposed labeling.

Regulatory Background

6/30/92 - Original NDA 50,679 submitted; contained efficacy studies AI411-118, 143 in support of an indication for use as empiric therapy in febrile neutropenia; AI411-137 submitted for safety assessment but not efficacy. Labeling proposed for this indication was as follows:

1/4/94 - Clinical review of original NDA 50,679 by William Erhardt, M.D. found:

AI411-118 - Equivalence not demonstrated between cefepime and control for empiric therapy of febrile neutropenia.

AI411-131 - Equivalence demonstrated between cefepime and control for empiric therapy of febrile neutropenia but with only 22 patients in cefepime arm; majority of patients at one center.

AI411-143 (open, noncomparative study) - Clinical response rate similar to comparative studies.

Dr. Erhardt concluded that the data were inadequate to show that cefepime is equivalent to control regimens in empiric therapy of febrile neutropenic patients. Subgroup analysis suggested that cefepime monotherapy is inferior to control regimens in empiric therapy of febrile neutropenic patients. The data suggested that cefepime may have a safety advantage over aminoglycosides.

1/4/94 - Applicant informed of these conclusions in teleconference; responded that they considered these data to be an "interim report" and that they planned to submit a SNDA for this indication by the end of 1994.

7/26/94 - Action letter for original NDA issued; stated that indication of febrile neutropenia has been found to be non-approvable; requirements for approval given as either:

One adequate, well-controlled study with evidence of effectiveness in at least three of the following: nosocomial pneumonia, complicated intra-abdominal infections, complicated skin and soft tissue infections, acute osteomyelitis, and acute bacterial arthritis[1]

or

Appropriate results from two independent, adequate and well-controlled studies.

[1] This recapitulates the language of the DAIDP Points to Consider. Of the indications listed, MAXIPIME® (cefepime) is currently approved for use in pneumonia (including nosocomial pneumonia), and uncomplicated (but not complicated) skin/skin structure/soft tissue infections.

5/17/96 - Supplement SE1-002 to NDA 50,679 submitted; contains nine efficacy studies (5 controlled monotherapy, 2 controlled combination, 2 non-comparative) in support of an indication for use as empiric therapy in febrile neutropenic patients.

Proposed labeling:

3/5/97 - Presentation to the AIDPAC of the preliminary FDA analysis of the five trials comparing cefepime monotherapy to either ceftazidime monotherapy or combination therapy, along with presentations by the sponsor of their analysis and by FDA consultants on scientific and clinical trial design issues relevant to the indication of febrile neutropenia. The AC discussed considerations related to the use of antibiotics for this indication and voted 7-0 that the data and analyses as presented support the claim of safety and effectiveness of Maxipime® for empiric therapy of febrile neutropenic patients.

APPEARS THIS WAY
ON ORIGINAL

4 CHEMISTRY, MANUFACTURING, AND CONTROLS

No new chemistry, manufacturing, and controls (CMC) data were submitted with this supplement. The reader is referred to CMC reviews 1-4 of the original NDA, by Dr. Suva Roy, for a fuller summary of CMC information .

The drug substance, cefepime hydrochloride (HCl), is a white to off-white crystalline solid. Its chemical name, structure, and molecular formula are shown in section 3 of this review. Cefepime HCl may exist as a *syn*- or *anti*-isomer, depending on the conformation of the methoxime group; the *syn*-isomer is the drug substance. It is freely soluble (>400 mg/ml) in aqueous solution at 23°C at a pH of 1.5 or greater.

Cefepime HCl is synthesized by

The maximum content of acetone, the primary residual organic solvent, is %.

Nonsterile drug substance is prepared at the following facilities:

Bristol-Myers Squibb Co. Bio/Chem Division 315 N. Thompson Road Syracuse, NY 13221-4755	Bristol-Myers Squibb S.p.A. Bio/Chem Division Sermonta Latina, Italy

Sterile drug substance is prepared at the following facilities:

Bristol-Myers Squibb S.p.A. Bio/Chem Division Sermonta Latina, Italy	Bristol-Myers Barceloneta Bio/Chem Division/Barceloneta Operations Carr No. 2 Km 45.4 Barceloneta, PR 00617

Drug product (cefepime HCl/L-arginine blend) is prepared at the following facilities:

Bristol-Myers Squibb, S.p.A. Sermonta Via del Murillo Latina, Italy	Bristol-Myers Barceloneta, Bio/Chem Division/Barceloneta Operations Carr No. 2 Km 45.4 Barceloneta, PR 00617

Drug product is filled, packaged, and labeled at the Barceloneta, PR facility, in vial sizes of 0.5 g, 1 g, and 2 g.

5 ANIMAL PHARMACOLOGY/TOXICOLOGY

No new animal pharmacologic or toxicologic data were submitted with this supplement. The reader is referred to the animal pharmacology/toxicology review of the original NDA, by Dr. Kumar Mainigi *et al.*, for a fuller summary of pharmacologic and toxicologic information.

Acute toxicity studies

In Sprague-Dawley rats, intravenous administration of cefepime causes a dose-dependent pressor response; at doses of 500 mg/kg or greater, this pressor response is followed by rapid systemic arterial collapse and death. High doses of cefepime also cause ataxia, respiratory distress, tremors, and seizures. LD_{50} values in rats are as follows: males, 1272 mg/kg; females, 1067 mg/kg.

Medical Officer's Comment

The dosage schedule proposed in this supplement represents a dose of 28.6 mg/kg for a 70 kg individual, and 40 mg/kg for a 50 kg individual.

Subacute/chronic/carcinogenicity studies

In a 26 week chronic toxicity study in dogs, cefepime caused thrombocytopenia, leukopenia, and severe anemia. Thrombocytopenia and leukopenia resolved by 2 weeks after discontinuation of drug; anemia resolved 7 weeks post-treatment. Rechallenge with cefepime resulted in more rapid reappearance of hematologic abnormalities.

No long-term carcinogenicity studies have been conducted on cefepime.

Reproduction studies

Cefepime is not embryocidal or teratogenic in rats at doses up to 1000 mg/kg/day, in mice at doses up to 1200 mg/kg/day, or in rabbits at doses up to 100 mg/kg/day.

Mutagenicity studies

Cefepime induces clastogenesis in primary lymphocytes cultured *in vitro* after 20 hours exposure, but not after 4 hours exposure.

6 MICROBIOLOGY

No new microbiologic data were submitted with this supplement. The reader is referred to the microbiology review of the original NDA, by Dr. Pandu Soprey, for a fuller summary of microbiologic information.

Cefepime is a semi-synthetic, broad spectrum cephalosporin antibiotic. It is sometimes referred to as a fourth-generation cephalosporin because of its antimicrobial spectrum, which is a function of its physicochemical and biochemical properties. Cefepime possesses an aminothiazole group, which enhances antipseudomonal activity. The presence of a zwitterionic methylpyrrolidino group results in high solubility in water and rapid penetration through bacterial cytoplasmic membranes.

Like other cephalosporins, cefepime binds to and inactivates bacterial penicillin-binding proteins (PBPs), which are serine proteases required for cell wall synthesis; inactivation of PBPs leads to inhibition of cell wall synthesis, autolysis, and cell death. Cefepime is thus bactericidal. For most eubacteria, the PBP in lowest abundance is PBP2; cefepime has substantially higher affinity than do other cephalosporins for this protein in *Escherichia coli* and *Enterobacter cloacae*. Thus, saturation of PBP2 sites by cefepime occurs at a relatively low drug concentration. Cefepime binds poorly to PBP2 of *Pseudomonas aeruginosa*, but does have a high affinity for *P. aeruginosa* PBP3.

In vitro, cefepime is active against most clinically relevant gram-negative aerobic bacteria, including most Enterobacteriaceae, ~90% of strains of *P. aeruginosa*, *Haemophilus influenzae* (both penicillinase-positive and negative), *Moraxella catarrhalis*, and *Acinetobacter lwoffi*. It is not active against non-*aeruginosa* species of *Pseudomonas*, and has only intermediate activity against *Acinetobacter anitratus* and *Xanthomonas maltophilia*.

Cefepime is active against many pathogenic gram-positive aerobic bacteria, including methicillin-susceptible strains of *Staphylococcus aureus*, ~90% of strains of *Staphylococcus epidermidis*, *Streptococcus pneumoniae* (including penicillin-resistant isolates of *S. pneumoniae*), streptococci from Lancefield groups A, B, C, D (non-enterococcal), F, and G, and viridans streptococci. Like other cephalosporins, it is not active against methicillin-resistant *S. aureus*, *Enterococcus* species or *Listeria monocytogenes*.

With regard to relevant anaerobic bacteria, cefepime is active against *Fusobacterium nucleatum*, *F. necrophorum*, and *Clostridium perfringens*. It is not active against *Clostridium difficile*, and has intermediate or no activity against *Bacteroides* species, except for *Bacteroides ureolyticus*; *Bacteroides fragilis*, in particular, is resistant to cefepime. Cefepime has only intermediate activity against *Peptostreptococcus* species.

Medical Officer's Comment

Cefepime is active against the majority of bacterial species likely to cause infection in neutropenic patients. However, it is not active against enterococci and methicillin-resistant S. aureus, *which are potentially important sources of bacterial infection in this patient population. In some settings, use of cephalosporins has been associated with an increased incidence of enterococcal superinfection.*

Cefepime's mechanism of action predicts that it should be bactericidal against susceptible species. This has been confirmed by time-kill analyses and determination of minimal bactericidal concentrations (MBCs). For gram-positive organisms, the MBC/MIC ratio is ~2, while for gram-negative organisms it ranges from
Bactericidal activity is less evident against methicillin-resistant or penicillinase-producing gram-positive staphylococci. Cefepime shows a dose-dependent post-antibiotic effect (PAE) against *E. coli*, *E. cloacae*, *K. pneumoniae*, *S. marcescens*, and *S. aureus*, but not against *P. aeruginosa*; the PAE, when present, appears to be 50-100% longer than that observed for ceftazidime.

Cefepime has been shown to be synergistic with aminoglycosides against some strains of gram-negative bacteria, but not consistently. Its action is antagonized by imipenem or polymyxin B. It does not affect opsonin-mediated phagocytosis of gram-negative bacteria, but in sub-MIC concentrations does increase the bactericidal effect of human serum against *P. aeruginosa.*

Cephalosporin resistance may arise due to bacterial synthesis of ß-lactamase; such synthesis may be constitutive or result from cephalosporin-induced derepression of ß-lactamase mRNA synthesis. Alternatively, mutations in the genes encoding PBPs can affect cephalosporin binding to these proteins, leading to resistance. Finally, decreased cell permeability to cephalosporins can lead to resistance.

Cefepime is not hydrolyzed by the major plasmid-mediated ß-lactamases, nor is it an effective inducer of ß-lactamase expression. Except for *P. aeruginosa*, cefepime is active against bacterial strains constitutively expressing a chromosomally-encoded ß-lactamase. Cefepime is also more likely to retain activity against bacteria which have acquired a plasmid-encoded ß-lactamase. Bacteria which are resistant to third generation cephalosporins such as ceftazidime generally remain susceptible to cefepime. Resistance to cefepime appears to require both decreased outer membrane permeability and high level cephalosporinase production. Selection for drug resistant isolates *in vitro* occurs at a lower rate for cefepime than for other cephalosporins. In a murine model of peritonitis, exposure of *P. aeruginosa* or *E. cloacae* to cefepime was much less likely to result in emergence of resistant isolates than was exposure to ceftriaxone.

Agar dilution, broth dilution, and macrotube broth dilution methods give similar results for assaying susceptibility to cefepime for a panel of reference strains. Susceptibility to cefepime has been defined as an MIC of $\leq$8 µg/mL, intermediate susceptibility as an MIC of 16 µg/mL, and resistance as an MIC of $\geq$32 µg/mL. Using a 30 µg cefepime disk, susceptibility testing by the Kirby-Bauer disk diffusion technique has been correlated with quantitative determination of MICs; breakpoints for disk diffusion susceptibility testing have been defined as a zone diameter of $\geq$18 mm for susceptibility, 15-17 mm for intermediate susceptibility, and $\leq$14 mm for resistance.

Cefepime has been demonstrated to have a protective effect in a number of animal models of infection. In particular, in mice with cyclophosphamide-induced neutropenia, cefepime was more active than ceftazidime or cefotaxime in the treatment of infections caused by Enterobacteriaceae, *P. aeruginosa*, or staphylococci.

7 HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

No new human pharmacokinetic or pharmacodynamic data were submitted with this supplement. The reader is referred to the biopharmaceutic review of the original NDA, by Dr. Ene Ette, for a fuller summary of biopharmaceutic information.

Cefepime is rapidly absorbed and distributed following parenteral administration. Bioavailability following intramuscular injection is 100%. The drug is 16-19% protein-bound in plasma. Cefepime is metabolized to N-methylpyrrolidine (NMP), which is converted to NMP-N-oxide. 88% of a dose of cefepime is excreted unchanged, 6.8% as NMP-N-oxide, 2.5% as the 7-epimer of cefepime, and <1% as NMP. These metabolites do not have significant anti-microbial activity. Excretion is primarily via renal filtration.

Typical values for relevant pharmacokinetic parameters for cefepime are shown in Table 7.1. These were determined in normal volunteers after intravenous injection of a single dose.

Table 7.1 Single dose pharmacokinetic data for cefepime[1]

Dose (mg)	C_{max} (µg/mL)	$t_{½}$ (h)	AUC_{inf} (µg•h/mL)	Vss (L)
500	39.1 ± 3.5	2.00 ± 0.38	70.8 ± 6.7	16.6 ± 2.5
1000	81.7 ± 5.1	2.47 ± 0.73	148.5 ± 15.1	17.9 ± 1.8
2000	163.9 ± 25.3	1.99 ± 0.21	284.8 ± 30.6	17.3 ± 1.2

The pharmacokinetic studies submitted with the original NDA have shown that C_{max} and AUC_{inf} are dose-proportional.

Special population studies have shown that after adjusting for creatinine clearance, age and gender do not affect cefepime pharmacokinetics. Peak plasma concentrations and the volume of distribution are not affected by renal insufficiency. There is a linear relationship between the clearance time for cefepime and creatinine clearance; $t_{½}$ is approximately 2.2 h in patients with normal renal function and 13 h in patients with end-stage renal disease. The drug is removed by hemodialysis (HD), with a $t_{½}$ of 2.3 h; a 3 h hemodialysis eliminates 68% of the drug. Continuous ambulatory peritoneal dialysis (CAPD) is less efficient at removing cefepime than HD (14.5 mL/min vs. 161 mL/min). Drug concentrations in dialysate remain above the MIC_{90} for clinically relevant organisms for at least 48 hours following a 2000 mg dose.

Medical Officer's Comment

These pharmacokinetic data suggest that at a dosage schedule of 2 g IV q8h, serum concentrations of cefepime will remain at or above the MIC_{90} for the majority of bacterial species likely to infect neutropenic patients.

Cefepime pharmacokinetics are not significantly altered in patients with serious bacterial infections or those with hepatic dysfunction. Co-administration of cefepime and amikacin does not change the pharmacokinetic profile of either drug.

[1] Data were taken from study AI411-158-001. Values are expressed as mean ± S.D.

8 HUMAN CLINICAL EXPERIENCE

Foreign Experience

Foreign marketing approvals for cefepime are shown in Table 8.1. Asterisks indicate countries in which cefepime is approved for empiric therapy of febrile neutropenia.

Table 8.1 Foreign marketing approvals for cefepime

COUNTRY	Status
Argentina*	Launched 1995
Aruba*	Registered
Australia*	Registered
Austria*	Registered
Bahrain*	Registered
Belgium*	Registered
Brazil*	Registered
Canada	Launched 1995
Chile*	Registered
Costa Rica*	Registered
Czech Republic*	Registered
Denmark*	Registered
Ecuador*	Registered
El Salvador*	Registered
France*	Launched 1993
Germany	Launched 1995
Greece	Pre-registration
Guatemala*	Registered
Honduras*	Registered
Hong Kong*	Launched 1996
Ireland*	Registered
Israel*	Registered
Italy*	Launched 1994
Japan	Launched 1995
Kuwait*	Registered
Luxembourg*	Registered
Mexico*	Registered
Netherlands	Launched 1994
Panama*	Registered
Peru*	Registered
Portugal*	Registered
Spain*	Registered
Sweden	Launched 1993
Switzerland*	Registered
Turkey*	Registered
United Kingdom*	Registered
Venezuela	Launched 1995

Cefepime has been approved for this indication in thirty countries, including European Union members, with the precise labeling varying from country to country. For example, in France, cefepime is labeled as indicated for treatment of febrile episodes in neutropenic adult patients (*les épisodes fébriles chez les patients neutropéniques*), with no further qualification. Cefepime is not known to have been withdrawn from the market or the subject of adverse regulatory action in other countries. Review of adverse drug reaction (ADR) reports from foreign sources does not reveal any ADRs not already described in the label, or unusual incidence of ADRs.

Domestic post-marketing experience

Maxipime® (cefepime) received final approval in this country in January, 1996, and was launched in August, 1996. Review of adverse drug ADR reports does not reveal any ADRs not described in the product label, or an increase in frequency of ADRs. No data have been submitted on emergence of resistance to cefepime in clinical use.

9 REVIEW OF CLINICAL STUDIES

Introduction

The review of New Drug Applications (NDAs) for empiric therapy of febrile neutropenia is complicated by two factors. First, this indication has not previously been granted by the Division of Anti-Infective Drug Products (DAIDP); thus, there is currently no anti-infective agent approved for the indication of febrile neutropenia. Although the labeling of some antibiotics carries usage statements which imply that these drugs may be suitable for this indication, the language is non-specific and does not provide an adequate regulatory basis for identifying these drugs as suitable comparators for a controlled trial of empiric therapy.

In general, the policy of the Center for Drug Evaluation and Research (CDER) is that when there is no FDA-approved agent for an indication, and an active agent is used as the comparator, the test agent must either 1) demonstrate statistical superiority to the active comparator for its efficacy to be established (i.e., the active comparator is treated as a placebo) or 2) demonstrate equivalence to an active comparator previously shown to be superior to placebo in the scientific literature. It is clear from the literature that empiric therapy of febrile neutropenia is superior to no therapy (Hathorn and Lyke 1997), and that the community standard of care is to employ empiric therapy in this setting. The sponsor has provided references in their submission to such literature. Thus, comparator regimens which are medically accepted may be considered valid as active controls for the purposes of reviewing the clinical trials contained in this submission. Following this logic, the test drug must show therapeutic equivalence to the comparator regimen to demonstrate efficacy, but statistical superiority is not required.

The combination regimens employed in these trials include monotherapy with ceftazidime, combinations of a ureidopenicillin and an aminoglycoside, and combinations of ceftazidime with vancomycin or amikacin. All of these represent clinically accepted regimens for empiric therapy of febrile neutropenic patients (Pizzo *et al.* 1986; Hathorn and Lyke 1997), and therefore are acceptable from a regulatory standpoint as active comparators. However, it is important to note that there are subpopulations of febrile neutropenic patients who are at particularly high risk for severe infection, for whom some regimens, such as ceftazidime monotherapy, may not be appropriate.

A second, and more fundamental problem, is the lack of consensus with respect to deciding which patients are evaluable for efficacy, and which endpoints are appropriate measures of outcome. These problems have complicated both clinical trial design and reporting of results (Pater and Weir 1986; Young 1988).

The major reason for this lack of consensus is that fever is not a specific marker of infection, yet is frequently the only marker available in this patient population. Patients who have a positive culture result or a clinically documented infection should generally be evaluable for efficacy; however, such patients may be in the minority in a clinical study of empiric therapy of febrile neutropenia. Many patients with neutropenia and fever will not have a clinically or microbiologically identifiable source of infection at presentation or at any point during their clinical course, and may in fact not have a infectious

source of fever. A substantial number of these patients will defervesce only after resolution of agranulocytosis, making it difficult to determine whether antibiotics or bone marrow recovery were responsible for improvement. However, such patients cannot be identified *a priori*, and institution of antibiotic therapy only for microbiologically or clinically documented infections carries an unacceptably high risk of mortality from infection (Hathorn and Lyke 1997).

Thus, the clinical imperative that fever be treated promptly may make it difficult to conclude that an antibiotic regimen is 'effective' in treating infection, because it is not always clear that infection was present at the outset. However, fever cannot be disregarded as a clinical parameter, since neutropenic patients with fever must be presumed to be infected until proven otherwise.

This paradox has been addressed in a variety of ways in the literature. Some authors (Pizzo *et al.* 1986) have advocated survival from infection as the primary outcome, since this is an incontrovertible measure of effectiveness. This approach does not consider modification of the original regimen to constitute failure, since prevention of early mortality is the major goal from this perspective. However, this approach does not take into account morbidity from persistent fever, including complications from repeated modifications of antibiotic regimens, and may obscure differences between antibiotic regimens (Elliott and Pater 1988). In addition, from a regulatory standpoint, this approach could potentially lead to regulatory decisions on empiric therapy for febrile neutropenia that are not based on clinical reality. For example, a febrile neutropenic patient who was treated empirically with penicillin and survived after addition of other antibiotics would be scored as a success under this approach. Thus, a trial of penicillin as empiric therapy that employed such a definition of success might show therapeutic equivalence between penicillin and a standard comparator regimen, supporting regulatory approval of penicillin for this indication; however, few clinicians, if any, would use penicillin for empiric therapy in this setting.

The alternative approach, that of considering defervescence as a primary outcome, is also problematic, for the reasons outlined above. In addition, this approach may lead to outcome decisions that are as paradoxical as the survival approach. For example, a patient who has fever alone, defervesces on empiric therapy, and subsequently develops an infection with an isolate with induced resistance to the original regimen would be considered a success, although from a clinical standpoint the patient may be worse off than if he had never received empiric therapy.

The definition of primary outcome has a direct effect on which patients will be considered evaluable for efficacy. For example, if one considers defervescence as the main endpoint, with modification of the empiric antibiotic regimen considered a treatment failure, then patients should receive the initial regimen for a minimum duration of time in order to be evaluable for efficacy. The minimum length of time that would be required for evaluability may vary between different studies. If one is simply examining survival, however, then a minimum duration of therapy may not be needed. Similarly, protocol definitions of infections or allowable modifications of the anti-microbial regimen that may occur during empiric therapy affect patient evaluability. For example, it is

not always clear whether neutropenic patients who have fever alone and receive both anti-bacterial agents and anti-fungal or anti-viral agents are evaluable, since such patients may have a non-bacterial infection.

The Infectious Diseases Society of America has published guidelines for the evaluation of anti-infective drugs for the empiric treatment of febrile episodes in neutropenic patients that address these issues of clinical trial design and the principles for evaluation of response to therapy (Hughes *et al.* 1992). They provide important guidance on aspects of optimal study design, including study population selection, inclusion and exclusion criteria, comparator selection, allowable modifications, endpoints, and methods of data analysis.

Although the IDSA guidelines are helpful in providing a framework for designing, performing, and analyzing studies in this area, many key issues remain unresolved from the regulatory standpoint. The questions of which primary and secondary endpoints should be emphasized in making regulatory decisions and which patients should be considered as evaluable in the review of NDAs for this indication remain incompletely answered. The Points to Consider (PTC) document issued by the Division of Anti-Infective Drug Products (DAIDP) does not explicitly address clinical trial designs and evaluability criteria, but it does suggest that for this indication, an application present data from at least one statistically adequate and well-controlled multicenter trial, along with previously established effectiveness for at least three specific deep infections (e.g., pneumonia, complicated urinary tract infections, complicated skin and skin structure infections).

In addressing the problems described above, three goals were paramount. First, consistent evaluability and efficacy criteria were needed that would allow review of studies with similar trial designs, both in this application as well as in future applications which might be submitted to the FDA. Second, the data had to be analyzed to determine the efficacy and safety of Maxipime® for empiric therapy for febrile neutropenic patients, relative to a clinically acceptable comparator. Finally, if consistent with approval, the data and analysis had to form the basis for construction of a clinically useful and scientifically sound label.

The strategy used to reach these goals centers around the observation by Hughes *et al.* (1992) that "... it is optimal to use multiple parameters for the assessment of [febrile neutropenic] patients, including clinical response to therapy, evidence of microbiologic efficacy, and survival." In addition, as pointed out by Sackett and Gent (1979), the nature of an evaluable population and the endpoints used to analyze that population depend on the question being asked of the data and the necessity of "avoiding specific bias". Thus, if one is asking whether an empiric regimen "works", it is important to define what one is asking of the drug: Should it treat the initial infection, prevent subsequent infections (i.e., provide prophylaxis), or simply protect against early mortality from infection? Furthermore, should one examine efficacy in a well-defined population, or in a study population that mirrors that found in the real world?

The review method, therefore, involved examination of the data from multiple perspectives. Evaluability criteria were designed, based on those used by the sponsor and

the available literature. Two sets of evaluability criteria were devised: a primary evaluability set, and a modified intent-to-treat (MITT) set; these are shown in Tables 9.1A and B, along with those used by the sponsor. The Medical Officer's set of primary evaluability criteria and those used by the sponsor were quite similar. Analysis of the evaluable subset data was undertaken to examine a population that was relatively homogeneous, excluding those patients with confounding factors. In contrast, analysis of the MITT population attempted to mimic "real world" situations found outside the clinical study setting (Viscoli *et al.* 1995), including those patients who were receiving treatment for pre-existing infection at the time that empiric therapy of febrile neutropenia was started.

Table 9.1A: Primary evaluability exclusion criteria

#	FDA	BMS
1	Not febrile at study entry[1]	Not febrile at study entry[1]
2	Not neutropenic within 2 d of study entry[2]	Not neutropenic[2]
3	Systemic ABx w/in 72 h of study entry	Systemic Abx within 72 h of study entry
4	Well-documented non-infectious cause of fever	Non-infectious cause of fever
5	Infection due to virus, fungus, AFB, parasite[3]	Infection due to virus, fungus, AFB, parasite
6	Final microbiologic outcome unavailable[4]	Major protocol violation
7	Final clinical outcome unavailable	Major protocol violation
8	ABx changed for clinical ADR	
9	Abx changed for laboratory ADR	
10	Discontinuation/modification prior to 72 h	Clinically unjustified modification prior to 72 h
11	Concomitant antibiotics in absence of failure	Concomitant Abx in absence of failure

Table 9.1B: Modified intent-to-treat (MITT) evaluability exclusion criteria

#	FDA	BMS
1	Not febrile at study entry[1]	Not febrile at study entry[1]
2	Not neutropenic within 2 d of study entry	Not neutropenic[2]
3	Well documented non-infectious cause of fever	Non-infectious cause of fever
4		Randomized but not treated (<1 dose of drug)
5		Systemic Abx within 72 h of study entry

[1] Oral temperature >38.3°C, or >38.1°C x 2.

[2] Absolute neutrophil count (ANC) < 500/μL.

[3] Patients with FUO were considered unevaluable if a non-antibacterial anti-microbial (e.g., amphotericin) was added prior to defervescence.

[4] Patient may have been evaluable clinically even if no follow-up cultures were obtained.

Episodes were assigned one of four different infection diagnoses:

1. Microbiologically defined infection (MDI) with bacteremia. For review purposes, any blood culture which grew a Gram-negative organism was regarded as evidence of bacteremia. The diagnosis of a Gram-positive bacteremia was made if one positive culture was obtained for a pathogenic Gram-positive organism (e.g., *Staphylococcus aureus*). For organisms which might represent a contaminant (e.g., *Staphylococcus epidermidis* or *Bacillus* species), at least two positive cultures (with all isolates showing the same antibiotic susceptibilities) within a 2 day period were required for this diagnosis, or a positive blood culture and a positive catheter tip culture.
2. MDI (without bacteremia). For review purposes, this diagnosis required a positive culture which either grew a pathogenic organism, or a culture growing a normally non-pathogenic organism (e.g., *S. epidermidis*) in a clinical setting consistent with the isolate representing true infection rather than contamination.
3. Clinically diagnosed infection (CDI). This diagnosis required a set of clinical findings compatible with infection at a specific site.
4. Fever of uncertain origin (FUO). Any febrile episode which did not mean the criteria in 1-3.

A fifth category, non-infectious fever (NIF), was used for patients who had convincing evidence of a non-infectious source of fever (e.g., deep venous thrombosis); such patients were considered unevaluable under both sets of evaluability criteria. Convincing evidence was considered to be pathologic or radiologic data consistent with this diagnosis, or an investigator's statement that provided a clinical rationale for this diagnosis.

Next, an approach similar to that used by Elliott and Pater (1988) was used. For evaluable episodes, clinical outcomes were coded using a numeric scheme, without classifying them initially as success or failure, as shown in Table 9.2. Definitions of response are shown in Table 9.3A; early response was defined as the response to empiric therapy at 72 h in the absence of modification. Different definitions of success were then devised, as shown in Table 9.3B. These correspond to specific clinical goals - treatment of the initial episode, prevention of subsequent febrile episodes or documented infection, and survival. Different codes were then scored as success or failure, using these different definitions.

To avoid bias during patient assessment and outcome analysis, three principles were consistently followed. First, patient assessment was performed by the Medical Officer in a blinded fashion, without knowledge of the treatment arm assignment. Second, given the difficult nature of clinical decision-making in managing the febrile neutropenic patient, the evaluability criteria and outcome definitions were used consistently, with as little application of subjective clinical judgment on the part of the reviewer as possible. If the data provided by the sponsor were insufficient to make an outcome assessment or infectious disease diagnosis, additional data were requested before assigning an outcome. Finally, in applying different endpoints, selection bias was minimized by holding the size of the patient population (either the evaluable subset or the MITT subset) constant.

For the primary analysis, definition 1B was applied to the evaluable subset. This defined success as resolution of the initial episode without modification or development of new episodes requiring modification, with the proviso that oral antibiotics could be used to complete therapy, and that addition of anti-fungal or anti-viral agents (after resolution of the initial episode if fever was the sole symptom) would not be considered a failure. Studies were analyzed with respect to all episodes, as well as first episodes only. Because recurrent episodes in the same patient may not be independent events, the primary analysis utilized first episodes rather than all episodes.

For the main MITT analysis, the strictest definition, 1A, was the outcome measure initially applied. However, for the two largest monotherapy trials, AI411-189 and AI411-204, response rates were determined for all outcome measures for the MITT population.

The primary analysis was used as the basis for regulatory decision-making for this application. The rationale for this was that this analysis used a definition of outcome which is consistent with the IDSA guidelines, combining three important outcome measures: the response for the initial episode, the occurrence of superinfection, and survival of infection. It is not, however, impossibly strict in that it allows for typical clinical practice (vis-à-vis use of post-therapy oral antimicrobials) and is consistent with the IDSA guidelines in allowing use of anti-fungal or anti-viral agents after resolution of the primary episode.

The other analyses, while not primary, provide important information on separate outcome measures such as the response for the initial episode, superinfections, and survival. The subdefinitions permit analysis of the contribution of post-therapy oral antimicrobials.

This regulatory approach was presented to the AIDPAC on March 5, 1997, and was endorsed by the committee members and FDA consultants present at the meeting.

Table 9.2. Clinical Outcomes Assigned by M.O.

1. Early response with complete resolution, no modification
   - 1.1 Microbiologically defined infection (MDI) with bacteremia
     - 1.11 Susceptible organism
     - 1.12 Resistant organism
   - 1.2 Microbiologically defined infection without bacteremia
     - 1.21 Susceptible organism
     - 1.22 Resistant organism
   - 1.3 Clinically defined infection (CDI)
     - 1.31 Pneumonia/Lower respiratory tract
     - 1.32 Upper respiratory tract
     - 1.33 Skin/soft tissue
     - 1.34 Gastrointestinal tract
     - 1.35 Other
   - 1.4 Fever of undefined origin (FUO)
     - 1.41 Probable infectious cause
     - 1.42 Well-documented non-infectious fever (NIF)
2. Early response, regimen subsequently modified, complete resolution
   - 2.1 MDI (same organism)
     - 2.11 Sensitive strain
     - 2.12 Resistant strain
     - 2.13 Unknown susceptibility
     - 2.14 Fungus
   - 2.2 MDI (different organism; includes *C. difficile* colitis)
     - 2.21 Sensitive strain
     - 2.22 Resistant strain
     - 2.23 Unknown susceptibility
     - 2.24 Fungus
   - 2.3 CDI
     - 2.31 Same CDI
     - 2.32 New CDI
   - 2.4 FUO
     - 2.41 While on initial regimen
     - 2.42 After initial regimen discontinued
3. Poor early response to 1° therapy with subsequent complete resolution
   - 3.1 Initial regimen not modified
     - 3.11 Poor microbiologic response
     - 3.12 Poor clinical response (other than persistent fever)
     - 3.13 Poor clinical response
     - 3.14 Persistent fever
   - 3.2 Initial regimen modified
     - 3.21 Poor microbiologic response; sensitive isolate
     - 3.22 Poor microbiologic response; resistant isolate
     - 3.23 Poor clinical response (other than persistent fever)
     - 3.24 Persistent fever
4. Death or unsatisfactory resolution
   - 4.1 Due to primary infection
     - 4.11 No modification of initial regimen
     - 4.12 Modification of initial regimen; resistance in Field 5
   - 4.2 Due to new infection
     - 4.21 No modification of initial regimen
     - 4.22 Modification of initial regimen
   - 4.3 Due to underlying disease
     - 4.31 No modification of initial regimen
     - 4.32 Modification of initial regimen
   - 4.4 Due to other cause
     - 4.41 No modification of initial regimen
     - 4.42 Modification of initial regimen
5. Other modifications of initial regimen
   - 5.1 Clinically unjustified modification
     - 5.11 At or after scheduled early response assessment
     - 5.12 1 day prior to scheduled early response assessment
     - 5.13 2 days prior to scheduled early response assessment
     - 5.14 3 days prior to scheduled early response assessment
   - 5.2 For adverse event
     - 5.21 Clinically and microbiologically not improved
     - 5.22 Clinically and microbiologically improved
6. Lost to follow-up
   - 6.1 Final microbiologic outcome unavailable
   - 6.2 Final clinical outcome unavailable
7. Other outcome not included above
   - 7.1 Infection due to fungus, virus, or parasite
   - 7.2 Well-documented non-infectious fever
   - 7.3 Non-study antibiotics within 72 h of study entry
   - 7.4 Not febrile and neutropenic at time of study entry

Table 9.3A. Definitions of Response			
	FDA 1° analysis	**FDA MITT analysis**	**Basic BMS definition[1]**
Clinical Response	All signs and symptoms eradicated, and cultures negative (for MDIs) with the initial therapy. No recurrence of infection apparent for at least 4-7 d after drug discontinuation	Same as FDA 1° analysis	Fever and clinical signs of infection and infection organism eradicated without change in study therapy. Response maintained for 5-7 days following completion of treatment
Non-response	Death, clinical deterioration or microbiologic failure on initial regimen; addition of new anti-bacterial for persistent symptoms or new infection; resistant isolate	Same or lack of follow-up data or discontinuation before completion due to adverse event or resistant isolate; discontinuation or modification at < 72 h; addition of antifungals, antivirals, or oral antibiotics	Death, no clinical response, deterioration, persistent fever or bacteremia (>24 h on therapy), clinical or microbiologic relapse within seven days post-treatment, isolation of an organism resistant to drug

Table 9.3B. Definitions of Success

Clinical improvement and sustained defervescence achieved without modification of treatment (successful treatment of primary episode without new episode).

A No other antibiotics were allowed

B Completion of therapy with an oral antibiotic agent allowed. Anti-fungal or antiviral agents allowed for microbiologically documented infections, or for other infections after resolution of the primary episode.

Clinical improvement and initial defervescence achieved without modification of treatment (successful treatment of primary episode). Categories A and B as above.

Survival from infection regardless of modification of treatment (reduction of mortality)

[1] BMS endpoints were similar for studies AI411-143, 158, and 186. Follow-up periods over all nine studies ranged from 3 to 7 days.

An overview of studies reviewed in this supplement is shown in Table 9.4. The studies fell into four groups:

1. Cefepime monotherapy compared to ceftazidime monotherapy (studies AI411-131, 189, and 204).
2. Cefepime monotherapy compared to a ß-lactam/aminoglycoside combination (studies AI411-118 and 137).
3. Cefepime in combination with amikacin (study AI411-186) or in combination with vancomycin (study AI411-198) compared with the corresponding ceftazidime combination.
4. Open-label, non-comparative studies (studies AI411-143 and 158).

Studies were analyzed individually. In addition, studies AI411-204 and -189, the largest trials in Study Group 1 (studies comparing cefepime monotherapy and ceftazidime monotherapy) were also pooled for analysis. Trials in Study Groups 2, 3, and 4, comprising the studies comparing cefepime monotherapy to combination therapy (AI411-118, -137), those comparing cefepime combination therapy to ceftazidime combination therapy (AI411-186, -198), and the open-label studies (AI411-143, -158 were not pooled for efficacy analysis because of significant differences in trial design and heterogeneity of treatment effect (see below).

Table 9.4 Study Designs - NDA 50,679/SE1-002[1]

	AI411-145	411-158	AI411-131	411-189	411-204	AI411-118	AI411-137	411-186	411-198
Type	Phase II	Phase II	Phase III	Phase III	Phase III	Phase III	Phase III	Phase III	Phase III
Design	Open	Open	Open Randomized	Open Randomized	Double-blind Randomized	Open Randomized	Open Randomized	Open Randomized	Open Randomized
Country/Continent	Europe	Netherlands	U.S.	Europe	U.S.	U.S.	U.S.	France	Belgium
Cefepime	2g q8h	2g q8h	2g q8h	2g q8h	2g q8h	2g q8h	2g q8h	2g q12h +Amikacin	2g q8h + Vancomycin
Comparator	N/A	N/A	Ceftazidime 2g q8h	Ceftazidime 2g q8h	Ceftazidime 2g q8h	Piperacillin/ Gentamicin	Mezlocillin Gentamicin	Ceftazidime 2g q8h +Amikacin	Ceftazidime 2g q8h + Vancomycin
Start Date	1-90	2-91	8-89	2-93	1-93	6-89	7-90	10-92	2-93
End Date	6-91	11-91	11-91	6-95	11-94	12-91	8-92	11-93	2-94
No. of Sites	2	1	2	15	11	2	1	31	4
Accrual	84	30	90	281	276	116	71	353	111
Cefepime	84	30	45	139	143	59	35	242	53
Control	---	---	45	142	133	57	36	111	58
Total Episodes	108	30	104	324	315	116	71	353	111
Cefepime	108	30	52	166	163	59	35	242	53
Control	---	---	52	158	152	57	36	111	58

[1] Shaded columns represent studies submitted with original NDA. Study AI411-137 was submitted with the original NDA only as part of the safety database.