Efficacy based on the causative pathogen

62 patients in the cefepime arm and 54 patients in the ceftazidime arm in the evaluable pooled population had microbiologically documented infections. Response rates (using definition 1B) for the most common causative bacterial pathogens are shown in Table 10.4. It should be emphasized that the studies were neither designed nor powered to demonstrate a difference in treatment effect between the arms with regard to specific pathogens.

Table 10.4 Response by causative pathogen

Pathogen	Cefepime			Ceftazidime			p-value*
	Success	Failure	Total	Success	Failure	Total	
E. coli	2	11	13	7	4	11	0.033
S. epidermidis	3	10	13	2	7	9	1.000
K. pneumoniae	2	3	5	3	4	7	1.000
P. aeruginosa	2	6	8	1	0	1	0.333
S. mitis	4	1	5	2	4	6	0.242
Enterococcus spp.	0	5	5	0	6	6	—
S. viridans	0	0	0	0	0	0	—
S. aureus	4	1	6	0	1	1	0.333

* By Fisher's exact test (two-tailed)

There was no statistically significant difference in response rates between the two treatment arms, except for *Escherichia coli*, which was the pathogen most frequently identified in MDIs. (It should be remembered that this is a post hoc analysis, with the potential for a type I error. The difference in response rates between treatment arms *for E. coli* infections may reflect noncomparability of the groups, rather than a true difference in response rates.) The most common reasons for treatment failure for *E. coli* infections in the cefepime arm were persistent fever (3 cases), a new microbiologic documented infection with a different organism (3 cases), and resistance of the original isolate (2 cases). There was one death due to primary infection with *E. coli* in the cefepime arm. Thus, the lack of equivalence for E. coli infections for cefepime reflected the occurrence of secondary infections which were not connected with the original infection. In other words, this outcome definition asks the drug to act not only as a therapeutic agent for the initial infection, but also as a prophylactic agent during therapy against a secondary infection, an event which is independent of the primary infection. If outcome measure 2 was used - that is, outcome of the primary infection without regard to subsequent infections - the response rates for E. coli infections were 8/11 (72.7%) for ceftazidime, and 7/13 (53.8%) for cefepime. The difference between response rates under outcome measure 2B was not statistically significant (p=0.422 by Fisher's exact test).

Final conclusions

The applicant has submitted seven studies, five of them controlled, assessing the efficacy of cefepime as monotherapy for febrile neutropenia. The two largest studies, AI411-204 and 189, were designed according to the IDSA guidelines, and are adequate and well-controlled studies as defined in 21 CFR 314.126. The other three monotherapy studies (AI411-131, 118, and 137), although designed and conducted prior to publication of the IDSA guidelines, also meet the definition of adequate and well-controlled studies.

Individually, results from AI411-204 and 189 do not show therapeutic equivalence between cefepime and the control regimen. However, the pooled results from studies AI411-204 and AI411-189, as assessed by a variety of outcome measures, and the results from study AI411-131, demonstrate therapeutic equivalence between cefepime monotherapy and ceftazidime monotherapy for empiric therapy of febrile neutropenia. This conclusion is further supported by the results from the studies comparing cefepime to combination therapy (AI411-118 and AI411-137), and the uncontrolled studies (AI411-143 and 158). Therefore, the sponsor has met the requirement stated in the action letter of July 26, 1994 for the original NDA (see section 3) of submitting results from two independent, adequate and well-controlled studies which demonstrate efficacy of cefepime for this indication.

The combination therapy studies (AI411-186 and AI411-198) were marked by problems in their conduct resulting in a large number of patients being unevaluable for efficacy. The data from these studies does not have sufficient power to demonstrate therapeutic equivalence between cefepime in combination with vancomycin or an aminoglycoside, and the corresponding ceftazidime combination. Thus, these studies were not adequate to demonstrate the efficacy of cefepime in combination with an aminoglycoside or glycopeptide for empiric therapy of febrile neutropenic patients.

In conclusion, the integrated analyses of efficacy and safety (see section 11) demonstrate that cefepime monotherapy is safe and effective for the empiric therapy of febrile episodes in neutropenic patients. The analyses do not demonstrate efficacy of cefepime in combination with an aminoglycoside or glycopeptide for this indication.

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11 INTEGRATED ANALYSIS OF SAFETY

Mortality

All cause mortality and deaths due to primary infection, secondary infections, underlying disease, and other causes were analyzed by treatment arm for all enrolled patients in Study Groups 1 and 2, as shown in Table 11.1.

Table 11.1. Mortality in monotherapy studies

Cause	Cefepime (N=475)	Control (N=455)	Overall (N=930)
All	40 (8.4%)	30 (6.4%)	70 (7.5%)
1° infection	10 (2.1%)	11 (2.4%)	21 (2.2%)
2° infection	12 (2.5%)	7 (1.5%)	19 (2.0%)
Underlying disease	17 (3.6%))	11 (2.4%)	28 (3.0%)
Other	1 (0.2%)	1 (0.2%)	2 (0.2%)

There did not appear to be a significant difference in mortality either overall or due to specific causes. Kaplan-Meier analysis did not reveal any significant differences between treatment arms with regard to time to death.

Adverse Events

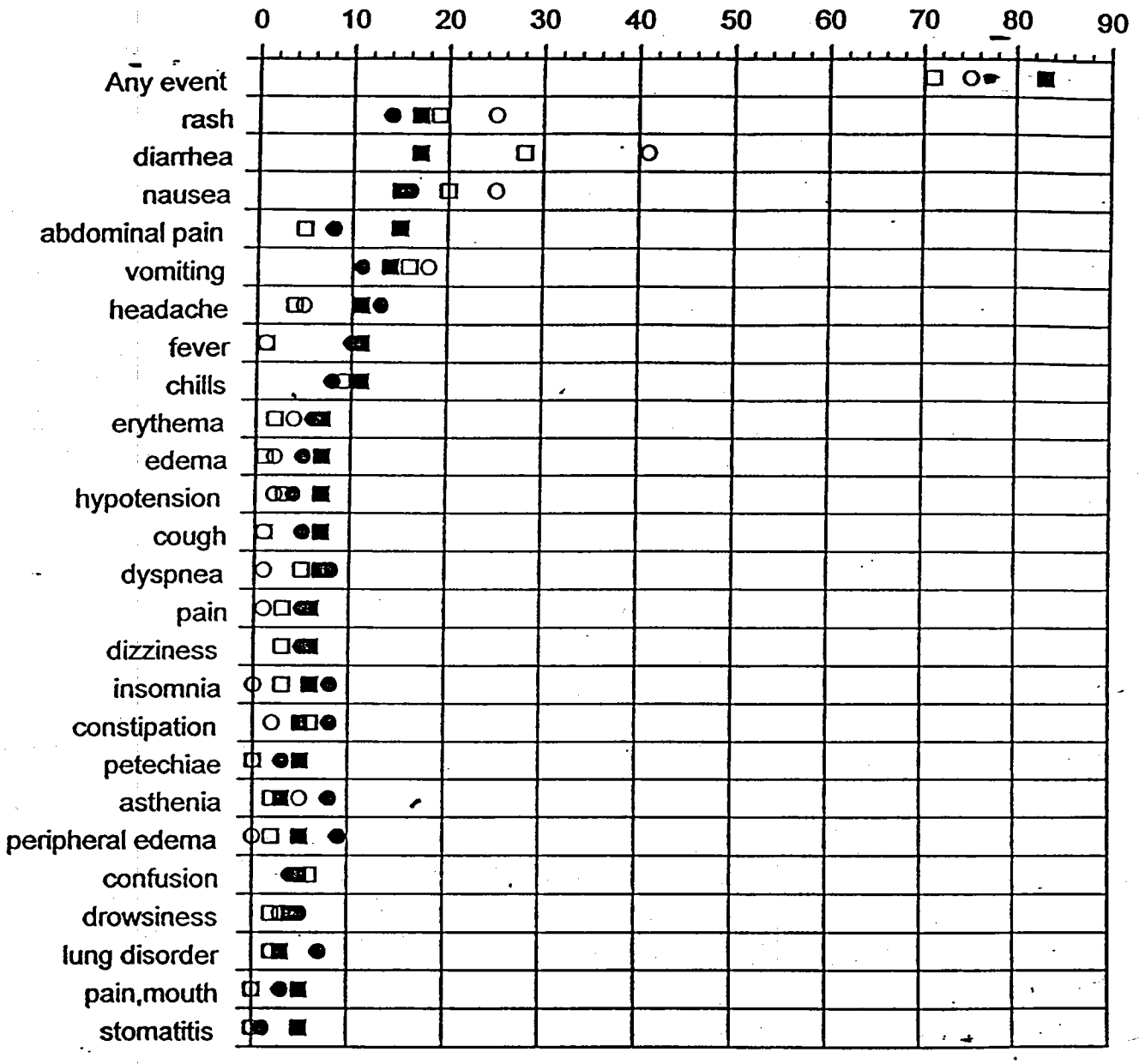
Very few adverse clinical events were reported in the 114 subjects accrued in the two non-comparative Phase II studies (AI411-143 and AI411-158; see Table 11.2 at the end of section 11). The most frequent were rash and diarrhea, which occurred in a total of 8 and 7 subjects, respectively. Erythema and nausea were reported in 3 subjects each. All the other adverse events occurred in single subjects; in most instances, they were considered to be not drug-related.

The comparative Phase III studies of cefepime monotherapy provide the core of the analysis of adverse clinical events (see Table 11.2 at the end of the section 11). A graphical presentation of adverse event rates is shown in Figure 3. Despite differences between the individual studies, the patterns of adverse events observed in all five trials were consistent and comparable across treatment groups. Overall, the most frequent adverse event was diarrhea, which was observed in about one-fifth of the subjects. The highest incidence was reported in two studies: 40% in the cefepime arm of AI411-131 and 75% in the combination arm of AI411-137. The other frequent adverse events were rash and gastrointestinal disturbances such as nausea, abdominal pain, and vomiting. A number of general symptoms, such as headache, fever, and chills, were also commonly reported. Some important differences were noted across the studies. The highest incidence of adverse events was seen in study AI411-137, which included many subjects who had undergone bone marrow transplantation, while the lowest was reported in studies AI411-118 and AI411-204, which had the highest proportion of subjects with solid tumors and therefore the shortest duration of neutropenia.

Medical Officer's Comment

Gastrointestinal disturbances are particularly common in patients undergoing treatment of malignancy, because of chemotherapy-induced destruction of gastrointestinal mucosa.

Figure 3. **Adverse Event Rates in Febrile Neutropenic patients**



■ Cefepime monotherapy
□ Cefepime combination therapy
● Ceftazidime
o Other combination therapy

In the pooled analysis of the comparative Phase III studies, the incidence of adverse clinical events was very similar in the cefepime and ceftazidime groups. The most frequent was diarrhea, which was observed in 17% of the subjects in both groups. Only a limited number of these episodes were considered to be drug-related, with an overall incidence of 2% for cefepime and 1% for ceftazidime. While other gastrointestinal disturbances, such as abdominal pain and vomiting, were somewhat more frequent in the cefepime group, the majority of these events were either not drug-related or were of unknown relationship to therapy. The incidence of the other most frequent adverse events was similar in both treatment groups. There were very few probably drug-related adverse events.

The comparison of cefepime to the two gentamicin-based combinations, AI411-118, and -137, yielded somewhat different results. There were differences detected between cefepime and the combinations for a number of adverse events, particularly gastrointestinal disturbances. The incidence of diarrhea was 41% in the combination group and 28% in the cefepime group. Nineteen percent of the diarrhea cases were felt to be probably drug-related, compared to 13% of the cases in the cefepime group. While the overall incidence of nausea was lower in the cefepime group, 20% compared to 25% in the combination group, the incidence of probably related nausea (9% versus 4%) was higher in the cefepime group, as was the incidence of vomiting (7% versus 2%). The pattern of other adverse events was similar between cefepime and the combinations and were similar to those events reported in the comparison of cefepime to ceftazidime.

The most frequent adverse events occurring the Phase III studies of cefepime in combination, AI411-186 and AI411-198. Both rash and diarrhea were less commonly reported in these studies than in those of cefepime monotherapy, while abnormal kidney function was more commonly reported. Of the 32 instances of abnormal kidney function in study AI411-186, only one, in the cefepime/amikacin group, was attributed to study therapy; four of the seven cases of abnormal kidney function that developed in study AI411-198 were attributed to study therapy, two in each treatment group. Mucositis and fever were the most frequently reported adverse events in studies AI411-186 and AI411-198, respectively.

Probably Drug-related Adverse Events

There was a total of 10 probably drug-related adverse events in the pooled analysis of the two non-comparative Phase II studies. They consisted primarily of rash (4 subjects) and diarrhea (3 subjects). Other probably drug-related adverse events were nausea, abdominal pain and erythema. These adverse events were generally mild; there were, however, 4 episodes of moderate rash.

Probably drug-related adverse events were also uncommon in the randomized trials. The most frequent was rash. The frequency of this adverse event was similar in all five studies, with the exception of study AI411-137, in which about one-third of the subjects experienced probably drug-related rash. The majority of the other probably drug-related events occurred in single subjects. There were, however, some notable exceptions, all occurring in study AI411-137. Diarrhea was common; a larger proportion of subjects in the combination group experienced this side effect (47% combinations versus 31% cefepime). The other exception was the high incidence of nausea (20% for cefepime and 8% for the combination) and vomiting (17% and 6%, respectively).

In the comparison of cefepime to ceftazidime, rash was the single most frequent probably drug-related adverse event. In most instances it was mild to moderate; in 3 subjects (2 cefepime and 1 ceftazidime) the rash was judged by the investigator to be severe. The incidence of other probably drug-related adverse events was similar between the cefepime and ceftazidime groups, with most rates being 1% or lower. Almost all events were mild to moderate, with the exception of 3 subjects who experienced severe adverse events other than rash.

In the comparison of cefepime to combination therapy, the most frequent probably drug-related adverse event was diarrhea, which was seen in 13% of cefepime subjects and 19% of the combination group. Diarrhea was usually mild to moderate; one subject in the combination group had diarrhea that was considered severe. The incidence of probably drug-related rash was 13% for cefepime and 14% in the combination group. Once again, most events were mild to moderate; three subjects (2 cefepime and 1 combination) developed severe rashes. With the exception of nausea and vomiting, all other adverse events were usually reported in single subjects. Of note, there were 2 episodes of severe kidney failure in the combination group. These episodes were felt to be related to the aminoglycoside used in the combination regimens.

Local Intolerance

Of the 114 subjects enrolled in the non-comparative trials, AI411-143 and AI411-158, only one experienced local intolerance of cefepime, in the form of phlebitis. In the overall analysis of the randomized trials of cefepime monotherapy, the overall incidence of local intolerance of study therapy was 6% for cefepime subjects and 4% for control subjects. Phlebitis and infiltration of the IV catheter site were the most common manifestations of intolerance. In the comparison of cefepime to ceftazidime, local intolerance was greatest in study AI411-131 and somewhat higher in the cefepime arm (16% versus 11% in the ceftazidime arm). Local intolerance was extremely uncommon in the comparison of cefepime to combination therapy.

Changes in Laboratory Values

Subjects with Normal Baseline Values

Laboratory abnormalities were frequently encountered in the non-comparative studies. Of the assessed subjects with normal baseline values, one half developed hypocalcemia and hyperphosphatemia. Thirty-one subjects (47%) developed elevations in ALT, nine of which were clinically relevant. Other abnormalities were seen in about one-quarter of the subjects.

Worsening of laboratory parameters in the randomized trials of cefepime monotherapy was infrequent and occurred in less than one-quarter of the subjects (see Table 11.4 at the end of section 11). As with adverse clinical events, there were some differences between individual studies. The highest incidence was seen in study AI411-131. In most cases there was consistency across the four other trials. In comparing cefepime to ceftazidime, very few differences were detected between the two treatment groups. Alteration in renal function, characterized by an increase in either BUN/blood urea or serum creatinine, was similar in the two treatment groups. These changes were generally minimal and rarely required therapeutic intervention. Overall, the incidence of increases in BUN/blood urea was 15% in both groups, while increases in serum creatinine occurred somewhat more frequently in the ceftazidime group (8% versus 5%). Changes in liver enzymes were also evenly distributed between the two treatment groups and occurred in approximately 20% of the subjects overall. Increases in bilirubin were more fre-

quent in the cefepime group (18% versus 8%). This difference was due in part to study AI411-189, where the respective incidences were 21% for cefepime and 7% for ceftazidime. Hypokalemia occurred in roughly one-third of the subjects, and were somewhat more frequent in the ceftazidime group. The changes were usually mild. In most instances, these changes in laboratory parameters could be attributed to the subjects' underlying medical condition as well as to the ancillary therapies they received. This is particularly true for those subjects who received total parenteral nutrition, large volumes of IV fluids, and chemotherapeutic agents known for their liver toxicity.

In comparing cefepime to the combinations of gentamicin and either mezlocillin or piperacillin, differences between the treatment groups were ascribed to the use of an aminoglycoside and consisted primarily of electrolyte imbalances and alterations in renal function. Overall, the incidence of BUN abnormalities was 5% for cefepime and 15% for the combinations, while the incidence of increased creatinine was 6% and 26%, respectively. No differences were seen with respect to hyponatremia (cefepime 28% and combinations 24%), there was a larger proportion of subjects in the combination group who experienced hypokalemia compared to the cefepime group (43% versus 26%).

Clinically relevant laboratory abnormalities were occasionally seen in the two non-comparative studies. The most frequent was an increase in ALT, which occurred in 9 (14%) of the 66 subjects who had normal baseline values. Clinically relevant hypocalcemia developed in one of ten subjects with normal baseline values. Other clinically relevant changes were usually seen in less than 5% of the subjects.

Clinically relevant abnormalities were also infrequent in the comparative studies of cefepime monotherapy. In the comparison of cefepime to ceftazidime, no difference between the two treatment groups could be detected. The highest incidence of clinically relevant abnormalities was noted for hypophosphatemia, with an incidence of 8% in the cefepime group and 10% in the ceftazidime group. Clinically relevant elevations in bilirubin were noted in about 3-4% of the subjects in both groups.

In the comparison of cefepime to combination therapy, the clinically relevant abnormalities follow the same pattern as in the comparison of cefepime to ceftazidime, with only one notable difference. In the combination group, 4 of 86 (5%) subjects developed clinically relevant increases in creatinine, compared to none in the cefepime group. As was discussed earlier, this difference is likely related to the use of an aminoglycoside in the combination regimens. All other laboratory abnormalities were similar in the two treatment groups.

Subjects with Abnormal Baseline Values

In the non-comparative studies, worsening of laboratory parameters was infrequent in subjects with abnormal baseline values. With the exception of uremia and hyperbilirubinemia, they usually occurred in less than 25% of the subjects.

There was a limited number of subjects with baseline laboratory abnormalities in the randomized trials of cefepime monotherapy. In the overall analysis of the worsening of laboratory values, there was little difference between the treatment groups. When present, the differences should be interpreted with caution due to the presence of pre-existing condition, as well as to the relatively small number of subjects in whom these abnormalities were described. The worsening

to clinically relevant abnormalities in those subjects with abnormal baseline values is somewhat higher than that seen in subjects with normal baseline values. Overall, there was little difference between the two treatment groups for any of the parameters.

There was no significant difference between treatment arms with respect time to recovery from neutropenia, as determined by Kaplan-Meier analysis (Figure 4).

Discontinuation Due to Adverse Events

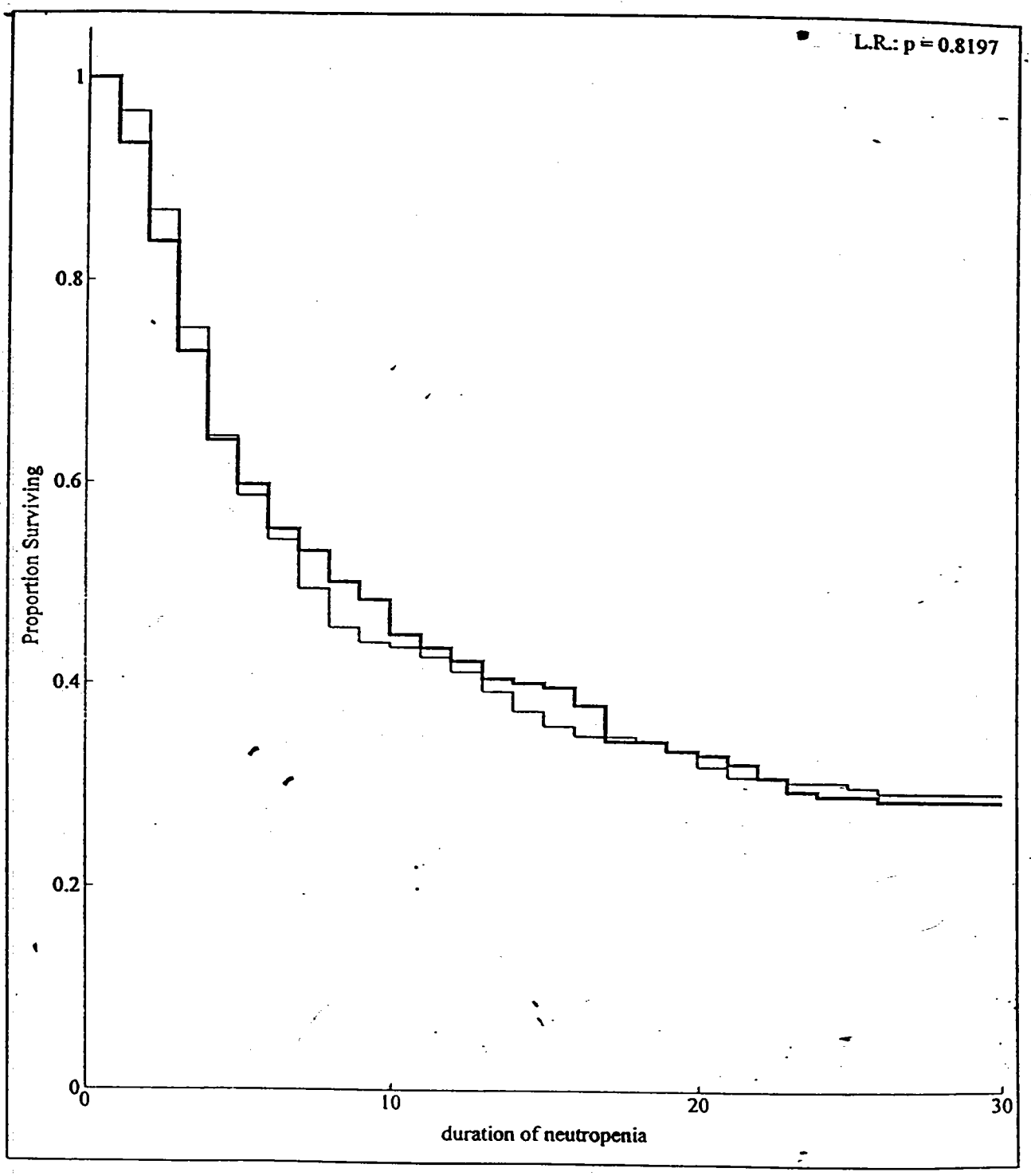
In the non-comparative studies, discontinuation of study drug due to adverse events was relatively uncommon. In both AI411-143 (3 subjects) and AI411-158 (2 subjects), rash was the most common adverse event leading to discontinuation; in four instances, rash was felt to be probably drug related. Other events included drug fever, nausea, and urticaria. In the randomized trials of cefepime monotherapy, the development of a skin rash was by far the most common adverse event that led to study drug discontinuation. In the analysis of cefepime versus ceftazidime, this occurred in 5% of the subjects in the cefepime group and 3% in the ceftazidime group. Of note, rash was associated with fever in one ceftazidime subject and with fever, nausea, and vomiting in one cefepime subject. The comparison of cefepime to combination therapy is notable because of study AI411-137, in which a total of 24 subjects (10 cefepime, 14 gentamicin/mezlocillin) discontinued study therapy because of skin rash. All other adverse events leading to discontinuation occurred in 1% of subjects. Only one subject, in the ceftazidime arm of study AI411-189, discontinued study therapy because of a laboratory abnormality. In this instance, an elevated serum ALT was felt to be possibly related to ceftazidime and eventually resolved within four weeks of discontinuing drug. In the five comparative studies, 51 of 72 adverse events leading to discontinuation were felt to be probably drug-related; forty-three of these were rash. The other eight included fever, nausea/vomiting, and diarrhea.

Other Studies Using Cefepime 2g q8h

The majority of the clinical experience in febrile neutropenia subjects was accumulated in protocols in which cefepime was given at a dose of 2g q8h. In addition, 932 subjects enrolled in seven trials conducted in other indications on this dosage regimen. The vast majority of these subjects were accrued in a large multicenter trial conducted in the U.S. It was designed to compare cefepime given at a dose of 2g q8h to ceftazidime given at the same dose-schedule. A total of 421 subjects were accrued in the cefepime arm and 419 in the ceftazidime group. Additional experience came from six small non-comparative studies. In three studies, subjects were treated with several different dosing regimens, but data included in this report specifically focus on those who received cefepime at the dose of 2g q8h. The 60 subjects accrued in these 3 studies had a variety of infections, including lower respiratory tract infections (LRTI), urinary tract infections (UTI), and skin and soft tissue infections (SSTI). Seventeen subjects were accrued in a small non-comparative study of subjects with endocarditis and the remaining fifteen subjects were included in two emergency release protocols.

Adverse events were reported infrequently in the 92 subjects included in the non-comparative studies of other indications. The most frequent event was rash, which was seen in 10 (11%) subjects. Other adverse events reported in 5% or more of subjects were headache, vomiting, nausea, and pruritus. There were very few adverse events of probable relationship to cefepime. These adverse events were usually mild to moderate in severity. The most frequent,

Figure 4. **Duration of neutropenia in evaluable patients for cefepime monotherapy trials with ceftazidime as the active control**



rash and pruritus, were reported in 4 subjects each. The other probably related adverse events seen in more than 2% of subjects were headache, dizziness, and taste alteration. All other events were described in single subjects.

In the randomized trial of other indications (study AI411-160), no differences could be detected between cefepime and ceftazidime. The most frequent adverse events were diarrhea (13% vs 12%) and headache (11% in both arms). Other frequently reported adverse events were nausea, peripheral edema, and hyperventilation. For most events, no difference between cefepime and ceftazidime could be detected, although the incidence of peripheral edema was somewhat greater in the cefepime group (7% versus 4%). These events were generally not related to study drug. They may reflect differences in the overall condition of the subjects accrued in the trial. Most of these events were mild to moderate in severity; one cefepime subject developed a rash which was considered severe.

Integrated Analysis of Adverse Events

Analysis by Indication

A total of 1,048 subjects were included in this integrated analysis of safety for cefepime administered at a dose of 2g q8h; 535 were included in the trials of febrile neutropenia and 513 in the trials of other indications. The most frequent adverse event was diarrhea, with an overall incidence of 14%, ranging from 17% in febrile neutropenia to 11% in other indications. Rash, gastrointestinal disturbances, and headache were the other frequently reported adverse events.

Differences between indications were apparent for a number of other adverse events. For instance, rash was seen in 15% of the febrile neutropenic subjects compared to 5% of the remaining subjects. It can be speculated that this difference may be related to specific characteristics of the neutropenic subjects, such as reactions to radiation therapy, graft versus host disease (GVHD), or other toxic effects of high-dose chemotherapeutic agents. Less striking differences were seen for nausea and vomiting. For most of the other adverse events, there were limited differences between the indications.

Analysis by Age

Our database included data on 318 elderly subjects (age >65 years). Most of these elderly were included in the non-neutropenic trials. Overall, there was little difference between the two age groups, irrespective of diagnosis. Two adverse events should, however, be highlighted. Rash was less frequent in elderly subjects regardless of the indication. In contrast, confusion was four times more frequent in the elderly non-neutropenic subjects compared to their younger counterparts (9% versus 2%).

Analysis by Gender

The analysis by gender did not conclusively demonstrate a higher incidence of any adverse events in males or females. The only adverse event for which differences were identified was headache, with an overall incidence of 12% in females and 7% in males. This difference was seen in both neutropenic and non-neutropenic subjects.

Analysis by Geographic Area

Adverse events were more frequently reported in studies conducted in North America compared to those conducted in Europe. A direct comparison can only be made for febrile neutropenic subjects. In this subgroup, the incidence of diarrhea was 24% in the North American

trials, compared to 9% in European studies. A similar difference was seen for almost all frequent adverse events. The difference described earlier between febrile neutropenic subjects and those treated for other indications was also seen if the analysis was restricted to North American trials.

Subclassification of adverse events possibly related to the study drug by indication, age, gender or geographic area

Limited data were available in subgroups when the adverse events that were possibly related to the study drug were considered. For this reason, discussion of this issue is of limited usefulness.

Table 11.2 All Adverse Events in Non-Comparative Febrile Neutropenia Trials

	Number (%) of Subjects (N =114)			
	Probably Related	Unknown	Not Related	Total
Any event	9(8)	3(3)	12(11)	24(21)
Rash	4(4)	1(1)	3(3)	8(7)
Diarrhea	3(3)	2(2)	2(2)	7(6)
Erythema	1(1)	---	2(2)	3 (3)
Nausea	1(1)	1(1)	1(1)	3(3)
Abdominal pain	1(1)	---	---	1(1)
Vomiting	---	---	1(1)	1(1)
Fever	---	---	1(1)	1(1)
Mucositis	---	---	1(1)	1 (1)
Bradycardia	---	---	1(1)	1(1)
Jaundice	---	---	1 (1)	1 (1)
Lung infiltrate	---	---	1(1)	1 (1)
Angioedema	---	---	1(1)	1(1)
Folliculitis	---	---	1(1)	1 (1)
Kidney function abnormal	---	---	1(1)	1(1)

Table 113: Most Frequent Adverse Events in Phase III Febrile Neutropenia Trials

	Number (%) of Subjects													
	Cefepime				Ceftazidime				Cefepime			Combination		
	131 (N=45)	189 (N=139)	204 (N=143)	Total (N=327)	131 (N=45)	189 (N=142)	204 (N=133)	Total (N=320)	118 (N=59)	137 (N=35)	Total (N=94)	118 (N=57)	137 (N=36)	Total (N=93)
Any event	40 (89)	98 (71)	134 (94)	272 (83)	42 (93)	101 (71)	122 (92)	265 (83)	33 (56)	34 (97)	67 (71)	34 (60)	36 (100)	70 (75)
Rash	18 (40)	18 (13)	20 (14)	56 (17)	17 (38)	14 (10)	15 (11)	46 (14)	3 (5)	15 (43)	18 (19)	4 (7)	19 (53)	23 (25)
Diarrhea	18 (40)	16 (12)	23 (16)	57 (17)	14 (31)	11 (8)	30 (23)	55 (17)	7 (12)	19 (54)	26 (28)	11 (19)	27 (75)	38 (41)
Nausea	12 (27)	8 (6)	28 (20)	48 (15)	16 (36)	8 (6)	27 (20)	51 (16)	7 (12)	12 (34)	19 (20)	8 (14)	15 (42)	23 (25)
Abdominal pain	12 (27)	12 (9)	24 (17)	48 (15)	7 (16)	7 (5)	13 (10)	27 (8)	2 (3)	3 (9)	5 (5)	4 (7)	3 (8)	7 (8)
Vomiting	11 (24)	9 (6)	25 (17)	45 (14)	12 (27)	7 (5)	17 (13)	36 (11)	5 (8)	10 (29)	15 (16)	3 (5)	14 (39)	17 (18)
Headache	11 (24)	7 (5)	19 (13)	37 (11)	9 (20)	15 (11)	17 (13)	41 (13)	2 (3)	2 (6)	4 (4)	4 (7)	1 (3)	5 (5)
Fever	2 (4)	5 (4)	29 (20)	36 (11)	1 (2)	10 (7)	22 (17)	33 (10)	---	1 (3)	1 (1)	1 (2)	---	1 (1)
Chills	13 (29)	1 (1)	23 (16)	37 (11)	10 (22)	1 (1)	16 (12)	27 (8)	5 (8)	3 (9)	8 (9)	2 (4)	8 (22)	10 (11)
Erythema	8 (18)	7 (5)	9 (7)	24 (7)	4 (9)	4 (3)	12 (9)	20 (6)	---	2 (6)	2 (2)	1 (2)	3 (8)	4 (4)
Edema	4 (9)	9 (6)	10 (7)	23 (7)	8 (18)	3 (2)	6 (5)	17 (5)	---	1 (3)	1 (1)	---	2 (6)	2 (2)
Hypotension	3 (7)	---	21 (15)	24 (7)	7 (16)	1 (1)	5 (/4)	13 (4)	3 (5)	---	3 (3)	1 (2)	1 (3)	2 (2)
Cough	2 (4)	11 (8)	11 (8)	24 (7)	4 (9)	3 (2)	9 (7)	16 (5)	---	1 (3)	1 (1)	1 (2)	---	1 (1)
Dyspnea	7 (16)	9 (6)	6 (4)	22 (7)	7 (16)	6 (4)	11 (8)	24 (8)	2 (3)	3 (9)	5 (5)	---	1 (3)	1 (1)
Pain	3 (7)	5 (4)	13 (12)	21 (6)	6 (13)	3 (2)	7 (5)	16 (5)	1 (2)	2 (6)	3 (3)	1 (1)	---	1 (1)

Table 11.3 (cont.)

Number (%) of Subjects

	Cefepime				Ceftazidime				Cefepime			Combination		
	131 (N=45)	189 (N=139)	204 (N=143)	Total (N=327)	131 (N=45)	189 (N=142)	204 (N=133)	Total (N=320)	118 (N=59)	137 (N=35)	Total (N=94)	118 (N=57)	137 (N=36)	Total (N=93)
Dizziness	9 (20)	1 (1)	11 (8)	21 (6)	5 (11)	---	10 (5)	15 (5)	2 (3)	1 (3)	3 (3)	2 (4)	3 (8)	5 (5)
Insomnia	4 (9)	---	15 (10)	19 (6)	3 (7)	1 (1)	20 (15)	24 (8)	---	3 (9)	3 (3)	---	---	---
Constipation	3 (7)	1 (1)	13 (9)	17 (5)	6 (13)	2 (1)	17 (13)	25 (8)	3 (5)	3 (9)	6 (6)	2 (4)	---	2 (2)
Petechiae	1 (2)	5 (4)	11 (8)	17 (5)	1 (2)	2 (1)	5 (4)	8 (3)	---	---	---	---	---	---
Asthenia	2 (4)	1 (1)	6 (4)	9 (3)	9 (20)	2 (1)	13 (10)	24 (8)	---	2 (6)	2 (2)	2 (4)	3 (8)	5 (5)
Peripheral edema	4 (9)	1 (1)	10 (7)	15 (5)	6 (13)	6 (4)	17 (13)	29 (9)	1 (2)	1 (3)	2 (2)	---	---	---
Confusion	4 (9)	2 (1)	9 (6)	15 (5)	8 (18)	---	5 (4)	13 (4)	2 (3)	4 (11)	6 (6)	1 (2)	4 (11)	5 (5)
Drowsiness	---	5 (4)	8 (6)	13 (4)	5 (11)	6 (4)	5 (4)	16 (5)	---	2 (6)	2 (2)	1 (2)	2 (6)	3 (3)
Lung disorder	---	1 (1)	9 (6)	10 (3)	2 (4)	3 (2)	16 (12)	21 (7)	---	2 (6)	2 (2)	---	2 (6)	2 (2)
Pain, mouth	3 (7)	---	12 (8)	15 (5)	4 (9)	---	4 (3)	8 (3)	---	---	---	---	---	---
Stomatitis	1 (2)	3 (2)	11 (8)	15 (5)	---	---	4 (3)	4 (1)	---	---	---	---	---	---

* Occurring in 5% of cefepime or ceftazidime subjects in the pooled analysis.

Table II.4: Laboratory Abnormalities in Cefepime Subjects with Normal Baseline Values

	Number of Subjects with Abnormal Values/Assessable Subjects (%)							
	F/N Non-Comparative	F/N vs. Ceftazidime	F/N vs. Combination	F/N Total	Other Non-Comparative	Other vs. Ceftazidime	Other Total	Total Cefepime 2g q8h
BUN	16/74 (22)	36/233 (15)	4/81 (5)	56/388 (14)	7/52 (13)	46/252 (18)	53/304 (17)	109/692 (16)
Creatinine	15/87 (17)	13/265 (5)	5/85 (6)	33/437 (8)	3/66 (5)	19/288 (7)	22/354 (6)	55/791 (7)
Alkaline phosphatase	18/69 (26)	42/190 (22)	13/61 (21)	73/320 (23)	11/40 (27)	41/214 (19)	52/254 (20)	125/574 (22)
AST/SGOT	24/80 (30)	34/189 (18)	8/59 (14)	66/328 (20)	9/40 (22)	67/224 (30)	76/264 (29)	142/592 (24)
ALT/SGPT	31/66 (47)	36/162 (22)	5/27 (19)	72/255 (28)	18/44 (41)	57/208 (27)	75/252 (30)	147/507 (29)
Bilirubin	12/54 (22)	34/191 (18)	8/63 (13)	54/308 (18)	2/51 (4)	14/273 (5)	16/324 (5)	70/632 (11)
Hyponatremia	20/63 (32)	44/183 (24)	14/50 (28)	78/296 (26)	7/46 (15)	59/267 (22)	66/313 (21)	144/609 (24)
Hypernatremia	4/63 (6)	7/183 (4)	2/50 (4)	13/296 (4)	1/46 (2)	12/267 (4)	13/313 (4)	26/609 (4)
Hypokalemia	21/67 (31)	68/233 (29)	21/82 (26)	110/382 (29)	10/67 (15)	52/302 (17)	62/369 (17)	172/751 (23)
Hyperkalemia	7/67 (10)	10/233 (4)	2/82 (2)	19/382 (5)	8/67 (12)	41/302 (14)	49/369 (13)	68/751 (9)
Hypocalcemia	5/10 (50)	54/130 (42)	0/39	59/179 (33)	3/38 (8)	66/159 (42)	69/197 (35)	128/376 (34)
Hypercalcemia	0/10	1/130 (1)	0/39	1/179 (1)	1/38 (3)	6/159 (4)	7/197 (4)	8/376 (2)
Hypophosphatemia	2/10 (20)	44/167 (26)	12/42 (29)	58/219 (26)	8/46 (17)	61/201 (30)	69/247 (28)	127/466 (27)
Hyperphosphatemia	5/10 (50)	14/167 (8)	7/42 (17)	26/219 (12)	10/46 (22)	40/201 (20)	50/247 (20)	60/466 (13)

12 RESISTANCE

In the pooled evaluable monotherapy database (studies AI411-204 and 189), out of 99 isolates which had cefepime susceptibilities determined, 15 (15.2%) were resistant to cefepime. 109 isolates had susceptibility to ceftazidime determined; of these, 23 (21.1%) were resistant to ceftazidime.

In all five monotherapy trials, the corresponding figures were 31/281 (11.0%) for cefepime and 47/291 (16.2%) for controls. These rates are consistent with previous literature on cephalosporin resistance.

In general, treatment failures due to resistance were distributed evenly across treatment arms. In addition, secondary infections due to resistant organisms appeared at equal frequency in both cefepime and control arms. Thus, cefepime was equivalent to comparator regimens with regard to resistance, both with respect to *in vitro* results and clinical outcomes.

13 LABELING RECOMMENDATIONS

Given the results of the monotherapy studies, approval of the claim for effectiveness of cefepime in monotherapy of febrile neutropenic patients is recommended (see section 14). The applicant has proposed use of the word in the labeling for cefepime to describe the outcome of empiric therapy of febrile neutropenia. As discussed in the introduction to the reviews of the clinical studies, a number of outcome measures can be applied to assess the response to therapy, all of which may be regarded as Furthermore, use of the word carries a promotional connotation that should be avoided. For these reasons, a more neutral term such as is recommended.

With regard to the claim for effectiveness of cefepime as combination therapy, a regulatory action of non-approval is recommended, since the combination therapy studies failed to demonstrate therapeutic equivalence between cefepime combination therapy and the comparator regimen. However, complete absence of any reference to combination therapy in the label is problematic, since monotherapy is not appropriate for a number of patients at high risk for infection (e.g., patients with hematologic malignancies, patients with prolonged or severe neutropenia or patients with a history of bone marrow transplantation) or those with severe infection (e.g., patients with hypotension at presentation). The discussion at the March 5, 1997 AIDPAC meeting made clear in such patients, empiric monotherapy for febrile neutropenia would be unsafe. Given that this indication has never been granted before by the Division, it is important to have any label for this indication be as specific as possible, not only with respect to the intended usage but to special situations as well. For this reason, description of situations in which monotherapy may not be appropriate would be justified. It would be necessary, however, to indicate that there are insufficient data to demonstrate the efficacy of cefepime monotherapy in these situations.

Finally, inclusion of additional information in the form of a clinical study section giving information on the pooled monotherapy studies (AI411-189 and AI411-204) is warranted. Given that much of this information has not been published, description of the studies on which approval is based (demographics, response rates, and subgroup analyses) would provide useful information to prescribing physicians. Inclusion of such information, however, not imply unsubstantiated claims. For example, description of the subgroup analyses should warn against drawing conclusions with respect to therapeutic equivalence between cefepime and ceftazidime,

since these were *post hoc* analyses. The combination therapy studies (AI411-186 and AI411-198) should not be included in a clinical study section, since they do not represent adequate and well-controlled studies supporting the efficacy of cefepime for this indication.

A proposal for the Indication and Usage statement and a Clinical Study section is as follows. The data in Table 1 is derived by pooling demographic data on evaluable patients in studies AI411-204 and AI411-189; the data in Table 2 is derived from Table 10.2C.

INDICATION AND USAGE

Empiric therapy for febrile neutropenia. Cefepime is indicated for empiric monotherapy of febrile neutropenia. Antibiotic monotherapy may not be appropriate in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or severe or prolonged neutropenia). Insufficient data exist to demonstrate the efficacy of cefepime monotherapy in such patients (See **CLINICAL STUDIES**).

CLINICAL STUDIES

The safety and efficacy of empiric cefepime monotherapy of febrile neutropenia have been assessed in two multi-center randomized trials comparing cefepime monotherapy (at a dose of 2 g IV q8h) to ceftazidime monotherapy (at a dose of 2 g IV q 8 h). These studies included 317 evaluable episodes. Table 1 describes the characteristics of the evaluable patient population.

Table 1. Demographics of evaluable patients

	Cefepime	Ceftazidime
Total	**164**	**153**
Median age (y)	56.0 (range, 18-82)	55.0 (range, 18-82)
Male	86 (52%)	85 (56%)
Female	78 (48%)	68 (44%)
Leukemia	65 (40%)	52 (34%)
Other hematologic malignancies	43 (26%)	36 (24%)
Solid tumor	54 (33%)	56 (37%)
Median ANC nadir (cells/μL)	20.0 (range, 0-500)	20.0 (range, 0-500)
Median duration of neutropenia (d)	6.0 (range, 0-39)	6.0 (range, 0-32)
Indwelling venous catheter	97 (59%)	86 (56%)
Prophylactic Abx	62 (38%)	64 (42%)
Bone marrow graft	9 (5%)	7 (5%)
SBP <90 mm Hg at entry	7 (4%)	2 (1%)

ANC, absolute neutrophil count; SBP, systolic blood pressure

Table 2 describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

Table 2. Pooled response rates for empiric therapy of febrile neutropenia

	% response	
Outcome measure	**Cefepime (N=164)**	**Ceftazidime (N=153)**
Primary episode resolved with no treatment modification, no new febrile episodes or infection, and oral antibiotics allowed for completion of treatment	51%	55%
Primary episode resolved with no treatment modification, no new febrile episodes or infection and no post-treatment oral antibiotics	34%	39%
Survival of infection, any treatment modification allowed	93%	97%
Primary episode resolved with no treatment modification and oral antibiotics allowed for completion of treatment	62%	67%
Primary episode resolved with no treatment modification and no post-treatment oral antibiotics	46%	51%

Insufficient data exist to draw conclusions regarding the efficacy of cefepime monotherapy in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or severe or prolonged neutropenia). No data are available in patients with septic shock.

14 RECOMMENDATIONS

1. The claim for effectiveness of cefepime as empiric monotherapy for febrile neutropenia at the proposed dosage of 2 g IV q8h is recommended for a regulatory action of approval, with appropriate labeling regarding lack of data regarding efficacy in patients at high risk for infection.
2. The claim of effectiveness of cefepime in combination with an aminoglycoside or glycopeptide for empiric therapy for febrile neutropenia is recommended for a regulatory action of non-approval.
3. A request for a phase IV commitment to a controlled trial comparing cefepime monotherapy to cefepime combination therapy is recommended.

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HFD-520/CSO/Duvall-Miller
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HFD-725/DivDir/Harkins
HFD-725/TL/Lin
HFD-725/Stat/Chakravarty
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