The extent of exposure to all study drugs (parenteral and oral) by treatment group for the treated population is displayed in the table below.

Extent of Exposure (Duration of Therapy) by Treatment Group
(Treated Population)

	MK-0826 (N=236)	Ceftriaxone (N=123)	Total (N=359)
Days on Study Therapy			
n	236	123	359
Mean	10.9	11.1	11.0
SD	3.8	3.5	3.7
Median	11.0	11.0	11.0
Range			
Days on Parenteral Therapy			
n	236	123	359
Mean	5.3	5.4	5.4
SD	2.7	2.7	2.7
Median	5.0	5.0	5.0
Range			
Days on IV Therapy			
n	236	123	359
Mean	5.1	5.2	5.2
SD	2.8	2.8	2.8
Median	4.0	4.0	4.0
Range			
Days on IM Therapy			
n	9	5	14
Mean	4.9	5.8	5.2
SD	2.5	1.1	2.1
Median	5.0	6.0	5.5
Range			
Days on Oral Therapy			
n	189	99	288
Mean	7.0	7.0	7.0
SD	2.7	2.4	2.6
Median	7.0	7.0	7.0
Range			
Days Missed Therapy			
n	5	8	13
Mean	1.0	1.8	1.5
SD	0.0	1.4	1.1
Median	1.0	1.0	1.0
Range			

IM = Intramuscular.
IV = Intravenous.
N = Total number of patients in each treatment group.
n = Total number of patients in category.
SD = Standard deviation.

(Applicant's Table 31, Volume 17 of 22, page 107)

Medical Officer's Comment: ***The 2 treatment groups were similar with respect to extent of exposure of total parenteral, IV parenteral, and oral therapy. The mean days of IM parenteral therapy were approximately one full day less for the MK-0826 group than the ceftriaxone group; however, the numbers of patients that received IM therapy are too small to draw meaningful conclusions about this difference.***

7.1.3.3.2 Deaths

There were 5 deaths in the MK-0826 group and 3 deaths in the ceftriaxone group among patients enrolled in Protocol 020 (2 deaths in the MK-0826 group and 3 deaths in the ceftriaxone group occurred during study therapy or the 14-day follow-up period). Three patients in the MK-0826 group (ANs 2964, 4200, and 4254) had adverse experiences beginning during parenteral therapy or follow-up and subsequently died outside of the 14-day follow-up period. The mortality rate

was similar between the 2 treatment groups. None of the deaths, nor the adverse experiences associated with the death, was considered study-drug related, by the Investigators or Applicant. Narratives of these deaths are found in Appendix 28. The table below lists all deaths reported during the entire study period, including 3 that occurred after the 14-day follow-up period in the MK-0826 group.

Listing of Patients With Adverse Experiences Resulting in Death During Entire Study (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day of Onset	Adverse Experience	Duration Of Adverse Experience	Intensity	Drug Relationship	Action Taken‡	Outcome
MK-0826												
3443	020005	M	Caucasian	97	Off drug	18	Death		Severe	Definitely not		
3272	020024	M	Caucasian	64	Off drug	27	Respiratory failure	2 days	Severe	Definitely not	None	Still present
					Off drug	28	Death		Severe	Definitely not		
2964§	020067	M	Caucasian	55	Off drug	31	Death		Severe	Definitely not		
					Off drug	31	Overdose, alcohol	1 day	Severe	Definitely not	None	Still present
4200§	020080	M	Hispanic	82	Off drug	22	Death		Severe	Definitely not		
					Off drug	22	Pneumonia, aspiration	7 hrs	Severe	Definitely not	None	Still present
4254§	020092	M	Hispanic	74	MK-0826 1 g	3	Septic shock/pneumonia	17 days	Severe	Definitely not	None	Still present
					Off drug	19	Death		Severe	Definitely not		
Ceftriaxone												
3191	020018	M	Caucasian	70	Ceftriaxone 1 g	2	Pneumonia, worsening	14 days	Severe	Definitely not	Discontinued	Still present
					Off drug	15	Death		Severe	Definitely not		
2753	020032	F	Caucasian	65	Cefuroxime 500 mg	11	Death		Severe	Definitely not		
					Cefuroxime 500 mg	11	Death, unknown cause	1 day	Severe	Definitely not	Discontinued	Still present
2888	020066	F	Caucasian	67	Off drug	22	Death		Severe	Definitely not		
					Off drug	22	Adult respiratory distress syndrome	1 day	Severe	Definitely not	None	Still present

† Displays any change of daily dose that occurs within the duration of the adverse experience.
‡ Action taken with regard to study drug therapy.
§ ANs 2964, 4200, and 4254 report a death that occurred more than 14 days after the discontinuation of study drug therapy.
"Entire Study" includes study therapy and entire follow-up period, not limited to 14 days.

(Applicant's Table 76, Volume 17 of 22, pages 199-200)

Medical Officer's Comment: ***The majority of deaths in the both treatment groups appear clearly related to failure of study therapy or underlying disease. The cause of death of patient AN 2753, although considered "Definitely Not" related to study therapy by the Investigator, is unexplained since the patient was found in cardiac arrest, but was thought to have improvement in CAP symptoms at the last visit prior to death.***

7.1.3.3.3 Other Serious Adverse Events

The following table displays, by body system, the number (percent) of patients with serious clinical adverse experiences with an incidence >0% in one or more treatment groups that occurred during the parenteral therapy period. Twenty-three (23) patients (9.7%) in the MK-0826 group and 9 patients (7.3%) in the ceftriaxone group had serious clinical adverse experiences. Five patients in the MK-0826 treatment group (ANs 3833, 3843, 4092, 4140, and 4200) and 2 patients in the ceftriaxone treatment group (ANs 3869 and 4038) had non fatal serious clinical adverse experiences during the parenteral therapy period that were considered by the investigator to be related to the study drug therapy. Narratives for these patients are provided in Appendix 27.

Number (%) of Patients With Serious Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	23	(9.7)	9	(7.3)
Patients with no adverse experience	213	(90.3)	114	(92.7)
Body as a Whole/Site Unspecified	**3**	**(1.3)**	**1**	**(0.8)**
Bacteremia	0	(0.0)	1	(0.8)
Infection	1	(0.4)	0	(0.0)
Shock, septic	1	(0.4)	0	(0.0)
Syncope	1	(0.4)	0	(0.0)
Cardiovascular System	**1**	**(0.4)**	**1**	**(0.8)**
Embolism/infarction, pulmonary	1	(0.4)	0	(0.0)
Heart failure	0	(0.0)	1	(0.8)
Digestive System	**4**	**(1.7)**	**2**	**(1.6)**
Cholecystitis	1	(0.4)	0	(0.0)
Colitis	1	(0.4)	0	(0.0)
Hemorrhage, anal/rectal	1	(0.4)	0	(0.0)
Hepatitis	0	(0.0)	1	(0.8)
Neoplasm, intestinal, malignant	0	(0.0)	1	(0.8)
Ulcer, gastric	1	(0.4)	0	(0.0)
Varices, esophageal	1	(0.4)	0	(0.0)
Hemic and Lymphatic System	**1**	**(0.4)**	**0**	**(0.0)**
Disseminated intravascular coagulopathy	1	(0.4)	0	(0.0)
Metabolic, Nutritional, Immune	**0**	**(0.0)**	**1**	**(0.8)**
Allergy	0	(0.0)	1	(0.8)
Musculoskeletal System	**0**	**(0.0)**	**1**	**(0.8)**
Fracture, femur, intertrochanter, left	0	(0.0)	1	(0.8)
Nervous System and Psychiatric Disorder	**3**	**(1.3)**	**0**	**(0.0)**
Alcohol withdrawal	1	(0.4)	0	(0.0)
Hallucinations	1	(0.4)	0	(0.0)
Seizure disorder	1	(0.4)	0	(0.0)

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Respiratory System	15	(6.4)	4	(3.3)
Bronchoconstriction	1	(0.4)	0	(0.0)
Chronic obstructive pulmonary disease	3	(1.3)	0	(0.0)
Dyspnea	0	(0.0)	1	(0.8)
Effusion, pleural	3	(1.3)	1	(0.8)
Empyema	2	(0.8)	0	(0.0)
Hypoxemia	1	(0.4)	0	(0.0)
Nodule, pulmonary	1	(0.4)	0	(0.0)
Pneumonia	2	(0.8)	1	(0.8)
Pneumonia, bacterial	1	(0.4)	0	(0.0)
Respiratory distress syndrome	2	(0.8)	0	(0.0)
Respiratory failure	1	(0.4)	2	(1.6)
Respiratory insufficiency	1	(0.4)	0	(0.0)
Skin and Skin Appendage	**1**	**(0.4)**	**0**	**(0.0)**
Infection, graft/implant	1	(0.4)	0	(0.0)
Special Senses	**1**	**(0.4)**	**0**	**(0.0)**
Herpes zoster, ophthalmic	1	(0.4)	0	(0.0)
Urogenital System	**1**	**(0.4)**	**0**	**(0.0)**
Renal insufficiency	1	(0.4)	0	(0.0)

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.

(Applicant's Table 72, Volume 17 of 22, pages 180-181)

Medical Officer's Comment: ***After reviewing the narratives and CRFs for these patients, the MO agrees with the Applicant's assessment that with the exception of those patients designated as having drug-related events, these reported serious adverse events are most likely due to efficacy failures or underlying diseases. Notable among the patients with drug-related serious adverse experiences is AN 3843. This elderly patient, with an underlying seizure disorder, had 2 seizures 1 day after dosage of MK-0826 was increased to 2 gms for intermediate penicillin resistant S. pneumoniae (a protocol violation since the protocol only allowed dosage increase for PRSP).***

There were a further 17 patients (7.2%) in the MK-0826 group and 13 patients (10.5%) in the ceftriaxone group with serious clinical adverse experiences that occurred after the parenteral therapy period. Eight patients (7 in the MK-0826 group and 1 in the ceftriaxone group) had serious clinical adverse experiences after the 14-day follow-up. Deaths were the most notable significant serious clinical adverse experiences occurring in the study therapy and follow-up period (5 in the MK-0826 group and 3 in the ceftriaxone group). The majority of the additional serious adverse experiences appear related to efficacy failure or complications of baseline conditions.

7.1.3.3.4 Dropouts

Thirteen (13) patients (5.5%) in the MK-0826 group and 7 patients (5.7%) in the ceftriaxone group discontinued parenteral therapy due to clinical adverse experiences. Six patients (ANs 3318, 3843, 3833, and 4200 in the MK-0826 group and ANs 3869 and 4038 in the ceftriaxone group) discontinued from parenteral therapy due to serious drug-related serious adverse events.

Two additional patients in each treatment group (ANs 3314 and 3318 in the MK-0826 group and ANs 2753 and3156 in the ceftriaxone group) discontinued from oral therapy due to clinical adverse experiences.

Patients discontinued from parenteral study therapy due to a clinical adverse experience are displayed in the following table.

Listing of Patients Discontinued Due to Clinical Adverse Experiences
During Parenteral Therapy and 14-Day Follow-Up Period
(Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose[1]	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance[2]	Intensity	Drug Relationship	Serious	Outcome
MK-0826													
3290	020026	M	Caucasian	64	MK-0826 1 g	1	Perversion, taste	10 hrs	1	Mild	Possibly	No	Recovered
3314[3]	020028	F	Caucasian	46	Off drug	5	Fever	4 days	8	Moderate	Definitely not	Yes	Recovered
					Off drug	8	Respiratory failure	24 days		Severe	Probably not	Yes	Recovered
3318	020028	F	Caucasian	37	Amoxicillin/ clavulanate 875 mg	11	Diarrhea	2 days	11	Severe	Probably	Yes	Recovered
3401	020032	M	Caucasian	66	MK-0826 1 g	3	Tachycardia	139 days	10	Mild	Definitely not	No	Still present
					MK-0826 1 g	3	Chronic obstructive pulmonary disease	139 days		Moderate	Definitely not	Yes	Still present
					MK-0826 1 g	3	Confusion	139 days		Mild	Definitely not	No	Still present
3482	020032	M	Caucasian	62	MK-0826 1 g	3	Tachypnea	139 days		Mild	Definitely not	No	Still present
3768	020036	F	Hispanic	79	MK-0826 1 g	2	Pneumonia	9 days	63	Moderate	Definitely not	No	Recovered
3722	020038	M	Caucasian	31	MK-0826 1 g	1	Bronchoconstriction	14 days	1	Severe	Definitely not	Yes	Recovered
3827	020054	M	Caucasian	57	MK-0826 2 g	5	Effusion, pleural	13 days	13	Severe	Probably not	No	Recovered
					MK-0826 1 g	3	Phlebitis-thrombophlebitis	13 days	15	Moderate	Definitely not	No	Recovered
					MK-0826 1 g	3	Embolism/infarction, pulmonary	13 days		Moderate	Definitely not	Yes	Recovered
					Off drug	4	Pericarditis	12 days		Moderate	Definitely not	Yes	Still present
					Off drug	4	Neoplasm, lung, malignant	12 days		Severe	Definitely not	Yes	Still present
3833	020054	F	Caucasian	72	MK-0826 1 g	8	Pneumonia	3 days	31	Moderate	Possibly	Yes	Recovered
3843	020054	M	Caucasian	76	MK-0826 2 g	10	Severe disorder	3 mins	30	Moderate	Possibly	Yes	Recovered
4026	020060	M	Caucasian	50	MK-0826 1 g	3	Pneumonia, bacterial	46 days	3	Severe	Probably not	Yes	Recovered
4113	020061	M	Caucasian	82	MK-0826 1 g	1	Respiratory insufficiency	2 days	1	Severe	Probably not	Yes	Recovered
4260	020080	M	Hispanic	82	MK-0826 0.5 g	2	Cholecystitis	21 days	10	Severe	Possibly	Yes	Still present
2898	020084	M	Black	48	MK-0826 0.5 g	1	Pneumonia	15 days	7	Severe	Probably not	Yes	Recovered
4298	020093	M	Mestizo	46	MK-0826 1 g	9	Effusion, pleural	92 days	10	Severe	Probably not	Yes	Still present
Ceftriaxone													
3156	020016	M	Caucasian	64	Amoxicillin/ clavulanate 1750 mg	4	Neoplasm, lung, malignant	4 days	6	Severe	Probably not	Yes	Still present
3191	020018	M	Caucasian	70	Ceftriaxone 1 g	2	Bacteremia	14 days	10	Moderate	Definitely not	Yes	Still present
3298	020026	F	Caucasian	74	Ceftriaxone 1 g	2	Pneumonia	14 days		Severe	Definitely not	Yes	Still present
2753	020032	F	Caucasian	65	Ceftriaxone 1 g	1	Dyspnea	9 days	1	Severe	Definitely not	Yes	Recovered
3400	020032	M	Caucasian	70	Ceftriaxone 1 g	1	Death	1 day	11	Severe	Definitely not	Yes	Still present
3456	020032	M	Caucasian	54	Ceftriaxone 1 g	1	Endocarditis	4 days	2	Severe	Definitely not	No	Still present
					Ceftriaxone 1 g	1	Hoarseness	3 days	34	Moderate	Probably	No	Recovered
					Ceftriaxone 1 g	1	Dyspnea	3 days		Moderate	Probably	No	Recovered
3869	020047	F	Caucasian	75	Ceftriaxone 1 g	1	Hot flashes	3 days		Moderate	Probably	No	Recovered
4038	020060	M	Caucasian	71	Ceftriaxone 1 g	2	Allergy	4 hrs	18	Severe	Probably	Yes	Recovered
2978	020073	M	Black	36	Ceftriaxone 1 g	2	Hepatitis	28 days	53	Severe	Probably	Yes	Recovered
					Ceftriaxone 1 g	2	Respiratory failure	11 days	16	Severe	Definitely not	Yes	Recovered

[1] Displays any change of daily dose that occurs within the duration of the adverse experience.
[2] Day of last scheduled clinical or laboratory assessment performed, relative to the first day of study drug therapy.
[3] Includes AN 3414, who was discontinued from study drug therapy due to adverse experiences with onset on the day after the last dose of oral study drug therapy.

(Applicant's Table 79, Volume 17 of 22, pages218-220)

Medical Officer's Comment: ***The reasons for discontinuation in both treatment groups, in both the parenteral study period and the study therapy and follow-up period, were primarily related to efficacy failure. Overall, the percentage of patients discontinued from study therapy was similar in both treatment groups. The percentage of patients discontinued due to drug-related adverse events was similar in both groups.***

7.1.3.3.5 Other Treatment Emergent Adverse Events

Overall 162 patients had clinical adverse experiences during the parenteral therapy period (109 [46.2%] in the MK-0826 group and 53 [43.1%] in the ceftriaxone group) and 214 patients had clinical adverse experiences during the study therapy and follow-up period (141 [59.7%] in the MK-0826 group and 73 [59.3%] in the ceftriaxone group).

Medical Officer's Comment: ***The Applicant displayed adverse events in tables broken down by ≥3% or ≥0%. In the MO's tables that follow, the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2%, according to the Applicant, during the parenteral therapy period are displayed. Tables with the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2% during the study therapy and follow-up period are displayed in Appendix 26.***

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2% in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	109	(46.2)	53	(43.1)
Patients with no adverse experience	127	(53.8)	70	(56.9)
Body as a Whole/Site Unspecified	**20**	**(8.5)**	**8**	**(6.5)**
Edema/swelling	7	(3.0)	5	(4.1)
Cardiovascular System	**22**	**(9.3)**	**17**	**(13.8)**
Infused vein complication	12	(5.1)	10	(8.1)
Digestive System	**42**	**(17.8)**	**20**	**(16.3)**
Constipation	15	(6.4)	3	(2.4)
Diarrhea	9	(3.8)	3	(2.4)
Nausea	7	(3.0)	5	(4.1)
Hemic and Lymphatic System	**3**	**(1.3)**	**3**	**(2.4)**
Metabolic, Nutritional, Immune	**3**	**(1.3)**	**3**	**(2.4)**
Musculoskeletal System	**7**	**(3.0)**	**4**	**(3.3)**
Nervous System and Psychiatric Disorder	**36**	**(15.3)**	**18**	**(14.6)**
Anxiety	4	(1.7)	3	(2.4)
Dizziness	5	(2.1)	1	(0.8)
Headache	10	(4.2)	5	(4.1)
Insomnia	10	(4.2)	9	(7.3)
Respiratory System	**33**	**(14.0)**	**12**	**(9.8)**
Chronic obstructive pulmonary disease	5	(2.1)	1	(0.8)
Effusion, pleural	9	(3.8)	1	(0.8)
Skin and Skin Appendage	**7**	**(3.0)**	**6**	**(4.9)**
Pruritus	3	(1.3)	3	(2.4)
Urogenital System	**6**	**(2.5)**	**6**	**(4.9)**

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.

(Modified Applicant's Table 142, Volume 17 of 22, pages 385-389)

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Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2% in One or More Treatment Groups) by Body System
During Parenteral Therapy (Treated Population)
Drug Related

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences†	36	(15.3)	19	(15.4)
Patients with no drug-related adverse experience	200	(84.7)	104	(84.6)
Cardiovascular System	**9**	**(3.8)**	**10**	**(8.1)**
Infused vein complication	8	(3.4)	9	(7.3)
Digestive System	**16**	**(6.8)**	**5**	**(4.1)**
Diarrhea	5	(2.1)	1	(0.8)
Nervous System and Psychiatric Disorder	**7**	**(3.0)**	**2**	**(1.6)**

† Determined by the investigator to be possibly, probably, or definitely drug related.
N = Total number of patients per treatment group.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had a drug-related adverse experience.
(Modified Applicant's Table 66, Volume 17 of 22, page 171)

Medical Officer's Comment: Diarrhea (2.1% vs 0.8%, MK-0826 vs ceftriaxone respectively), overall Digestive System disorders (6.8% vs 4.1%, MK-0826 vs ceftriaxone respectively), and overall disorders of the Nervous System and Psychiatric Disorders (3.0% vs 1.6%, MK-0826 vs ceftriaxone respectively) were the only drug-related clinical adverse experiences that occurred in a higher percentage of patients in the MK-0826 group.

7.1.3.3.6 Laboratory Findings

Of the patients in the treated population, 48 (21.4%) in the MK-0826 group and 29 (24.6%) in the ceftriaxone group had a laboratory adverse experience during parenteral therapy. The most common laboratory adverse experiences were increased ALT (8.7% of patient treated with MK-0826 and 8.4% of patients treated with ceftriaxone) and increased AST (8.5% of patients treated with MK-0826 and 11.5% of patients treated with ceftriaxone). Increased serum alkaline phosphatase was reported in 9 (4.3%) patients in the MK-0826 group and in no patients in the ceftriaxone group. Increased platelet counts were reported in 14 (6.4%) patients in the MK-0826 group and 1 (0.9%) patient in the ceftriaxone group. The tables below display the number (percent) of patients with specific laboratory adverse experiences with an incidence ≥3% in one or more treatment groups, by laboratory test category, occurring during parenteral therapy and the number (percent) of patients with specific drug-related laboratory adverse experiences with an incidence ≥1% in one or more treatment groups by laboratory test category occurring during parenteral therapy.

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by Laboratory Test Category During Parenteral Therapy (Treated Population)

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	48/224	(21.4)	29/118	(24.6)
Patients with no adverse experience	176/224	(78.6)	89/118	(75.4)
Blood Chemistry	**35/222**	**(15.8)**	**24/117**	**(20.5)**
ALT increased	18/207	(8.7)	9/107	(8.4)
AST increased	18/213	(8.5)	13/113	(11.5)
Blood urea increased	1/7	(14.3)	0/4	(0.0)
BUN increased	3/200	(1.5)	4/101	(4.0)
Haptoglobin increased	1/1	(100.0)	0/0	(0.0)
Serum alkaline phosphatase increased	9/211	(4.3)	0/111	(0.0)
Serum CPK increased	1/1	(100.0)	0/0	(0.0)
Serum GGT increased	1/1	(100.0)	1/1	(100.0)
Serum LDH increased	3/3	(100.0)	2/2	(100.0)
Serum magnesium decreased	0/0	(0.0)	1/1	(100.0)
Serum phosphate decreased	1/1	(100.0)	1/1	(100.0)
Serum prealbumin decreased	1/1	(100.0)	0/0	(0.0)
Serum uric acid decreased	0/0	(0.0)	1/1	(100.0)
Hematology	**25/222**	**(11.3)**	**10/116**	**(8.6)**
Eosinophils increased	2/216	(0.9)	4/109	(3.7)
Fibrinogen increased	1/1	(100.0)	0/0	(0.0)
Hematocrit decreased	7/221	(3.2)	3/116	(2.6)
Hemoglobin decreased	9/221	(4.1)	4/116	(3.4)
Platelet count increased	14/220	(6.4)	1/116	(0.9)
Urinalysis	**9/186**	**(4.8)**	**4/99**	**(4.0)**
Urine yeast, nondiagnostic	2/2	(100.0)	0/0	(0.0)

N = Total number of patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All categories are listed in which at least 1 patient had an adverse experience.

(Applicant's Table 81, Volume 17 of 22, page 225)

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Number (%) of Patients With Specific Laboratory Adverse Experiences
(Incidence ≥1% in One or More Treatment Groups) by Laboratory Test Category
During Parenteral Therapy
(Treated Population)
Drug Related

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n/m	(%)	n/m	(%)
Patients with one or more drug-related† adverse experiences	26/224	(11.6)	15/118	(12.7)
Patients with no drug-related† adverse experience	198/224	(88.4)	103/118	(87.3)
Blood Chemistry	**17/222**	**(7.7)**	**9/117**	**(7.7)**
ALT increased	13/207	(6.3)	6/107	(5.6)
AST increased	12/213	(5.6)	8/113	(7.1)
BUN increased	1/200	(0.5)	1/101	(1.0)
Indirect serum bilirubin increased	1/92	(1.1)	0/46	(0.0)
Serum alkaline phosphatase increased	7/211	(3.3)	0/111	(0.0)
Serum CPK increased	1/1	(100.0)	0/0	(0.0)
Serum GGT increased	1/1	(100.0)	0/1	(0.0)
Serum LDH increased	1/3	(33.3)	0/2	(0.0)
Hematology	**8/222**	**(3.6)**	**4/116**	**(3.4)**
Eosinophils increased	1/216	(0.5)	3/109	(2.8)
Platelet count increased	6/220	(2.7)	0/116	(0.0)
Urinalysis	**5/186**	**(2.7)**	**4/99**	**(4.0)**
Urine bacteria increased	2/173	(1.2)	2/92	(2.2)
Urine WBCs increased	0/173	(0.0)	1/92	(1.1)
Urine yeast present	1/173	(0.6)	1/92	(1.1)
Urine yeast, nondiagnostic	2/2	(100.0)	0/0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
N = Total number of patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All categories are listed in which at least 1 patient had a drug-related adverse experience.

(Applicant's Table 82, Volume 17 of 22, page 227)

Medical Officer's Comment: ***In both the all and drug-related adverse events displays, ALT and AST elevations were similar in both treatment groups. Alkaline phosphatase was more frequently elevated in the MK-0826 group; however, the MO agrees with the Applicant that the alkaline phosphatase elevations were either associated with increased levels at baseline and/or the increase in alkaline phosphatase accompanied increased transaminases. Platelets were also more frequently increased in the MK-0826 group; however the MO finds the Applicant's explanation that the thrombocytosis appeared to be consistent with the degree of underlying inflammation, less plausible.***

Of treated patients with at least 1 laboratory test, 59 (25.7%) in the MK-0826 group and 37 (30.6%) in the ceftriaxone group had a laboratory adverse experience during the study therapy and the follow-up period. Of these, adverse experiences occurred in 48 patients in the MK-0826 group and in 29 patients in

the ceftriaxone group during the parenteral therapy period. There were 28 (12.2%) patients in the MK-0826 group and 18 (14.9%) patients in the ceftriaxone group who had drug-related laboratory adverse experiences. Of these, 26 patients in the MK-0826 group and 15 patients in the ceftriaxone group had a drug-related adverse experience during the parenteral therapy period. As was seen during the parenteral therapy period, the most common laboratory adverse experiences were increased ALT and AST (similarly in both groups) and increased alkaline phoshatase and increased platelets (more commonly in the MK-0826 group).

Serious laboratory adverse experiences were reported in 2 patients (ANs 3442 and 4219) in the MK-0826 group and no patients in the ceftriaxone group during the parenteral period. One patient (AN 4211) in the ceftriaxone group discontinued parenteral therapy due to a laboratory adverse event. One patient (AN 4219) in the MK-0826 group had a serious drug-related laboratory adverse experience. The Applicant's narrative of this patient is listed below.

(AN 4219)
A 51-year-old female with bronchoconstriction, COPD, gastric ulcer, hypertension, and a history of urinary incontinence, renal disorder, and smoking began therapy with MK-0826 for the treatment of CAP. At baseline, the patient's AST was 27 U/L (normal range 10 U/L to 31 U/L) and ALT was 28 U/L (normal range 9 U/L to 36 U/L). On Study Day 5, the patient's AST (88 U/L) and ALT (116 U/L) were increased. On Study Day 6, IV therapy was completed and the patient was switched to oral therapy with amoxicillin/clavulanate as per protocol until completion on Study Day 10. Subsequently, the transaminases did return to within normal range. In the opinion of the investigator, the increased AST and ALT levels were probably related to study drug therapy.

***Medical Officer's Comment:** The MO has reviewed the narratives and CRFs for these patients and agrees with the Applicant's presentation of drug relatedness.*

In the study therapy and follow-up period there were 3 additional patients (AN 3318 in the MK-0826 group and ANs 3097 and 2978 in the ceftriaxone group) that had serious laboratory adverse experiences. The events in both of the patients in the ceftriaxone group were considered to be drug-related (increased AST, ALT, and LDH in one patient and C. difficile test positive in one patient). The patient in the MK-0826 had an elevated platelet count, occurring during the off drug period that was felt to be "Definitely not" related to study therapy by the Investigator.

Overall, the proportions of serious laboratory- and serious drug-related laboratory adverse events were similar for the two treatment groups.

7.1.3.3.7 Assessment of Tolerability

An assessment of tolerability at the IV and IM study drug administration sites was performed daily while the patient was on study therapy. The intensity of specified local administration-related symptoms was rated as mild, moderate, or severe. Of patients who experienced one or more local reactions at the IV infusion site, 42/233 (18.0%) were in the MK-0826 group and 27/133 (22.0%) were in the ceftriaxone group. If local intolerance was felt by the Investigator to reach the level of a clinical adverse experience, the adverse experience was reported as a clinical syndrome (e.g. local phlebitis/thrombophlebitis) and was displayed as "infused vein complication" in the counts of clinical adverse experiences. A

clinical adverse experience of "infused vein complication" was reported for 12/236 (5.1%) of patients in the MK-0826 group and 10/123 (8.1%) of patients in the ceftriaxone group.

Nine patients in the MK-0826 group and 5 patients in the ceftriaxone group received at least one dose of IM parenteral therapy. There were no reported local reactions for any of these patients.

The following table presents the proportions of patients reporting any local reactions and the 95% CI of (-12.7, 4.9) about the difference.

Number (%) of Patients With Local Reaction Symptoms
During Parenteral Therapy
(Treated Population)

	Treatment Group						Difference (A - B)
	MK-0826 (A) (N=236)			Ceftriaxone 1g (B) (N=123)			
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)	% (95% CI)
Patients with one or more symptoms	42/233	(18.0%)	(13.1, 23.0)	27/123	(22.0%)	(14.6, 29.3)	-3.9 (-12.7, 4.9)
Patients with one or more symptoms of moderate-to-severe intensity	16/233	(6.9%)	(3.6, 10.1)	13/123	(10.6%)	(5.1, 16.0)	-3.7 (-10.0, 2.6)

N = Number of treated patients in each treatment group.
n/m = Number of patients reporting a tolerability symptom / number of patients with an assessment. Patients with an assessment "Not Done" are not counted.
CI = Confidence interval.

(Applicant's Table 93, Volume 17 of 22, page 245)

Medical Officer's Comment: ***Overall the rates of local reactions of any intensity were similar in the 2 treatment groups.***

7.1.3.3.8 Adverse Experiences of Special Interest

Four adverse experiences were prespecified for more detailed review because of preclinical findings (neutropenia), adverse experiences associated with β-lactam antibiotics as a class (liver function elevations and rash), and adverse experiences associated with other carbapenem antimicrobials (seizures).

Seizures

One patient (AN 3843) in the MK-0826 had a seizure, while on parenteral therapy, that was judged by the Investigator to be study drug-related. This patient was previously described in Section 7.1.3.3.3 of this review.

Neutropenia/Liver Enzyme Elevations

In addition to reviewing investigator-reported laboratory adverse experiences, the Applicant performed an assessment of the relative laboratory safety of each treatment group by using predefined Clinically Significant Laboratory Abnormalities (CSLAs) for specified tests and identifying patients whose worst

laboratory value represented a worsening from baseline and met the criteria for a CSLA. In order to be considered in the analysis for CSLAs, patients had to have a baseline laboratory value, at least 1 postbaseline laboratory test and have normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin the CSLA criteria were defined in terms of a fixed bound. For creatinine, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase, the CSLA criteria were defined in terms of a fixed bound greater than the upper limit of normal (ULN). The following table displays CSLAs for neutropenia and liver function assays during the parenteral therapy period and during the total study therapy plus the follow-up period.

Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group

Laboratory Test	CSLA Criteria	During Parenteral Therapy				During Study Therapy and Follow-up			
		Number (%) with CSLA				Number (%) with CSLA			
		MK-0826 (N=236)		Ceftriaxone (N=123)		MK-0826 (N=242)		Ceftriaxone (N=256)	
		n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Absolute neutrophils (cells/μL)	<1800	3/201	1.5	0/103	0.0	8/211	3.8	1/111	0.9
	<1000	0/201	0.0	0/103	0.0	1/211	0.5	0/111	0.0
ALT (U/L)	>2.5 x ULN	14/196	7.1	9/98	9.2	19/210	9.0	10/104	9.6
	>5 x ULN	1/196	0.5	3/98	3.1	3/210	1.4	3/104	2.9
AST (U/L)	>2.5 x ULN	15/207	7.2	5/106	4.7	18/220	8.2	5/111	4.5
	>5 x ULN	5/207	2.4	2/106	1.9	6/220	2.7	2/111	1.8
Direct serum bilirubin (mg/dL)	>1.5 x ULN	5/95	5.3	1/48	2.1	6/108	5.6	2/51	3.9
	>2.5 x ULN	3/95	3.2	0/48	0.0	3/108	2.8	0/51	0.0
Hematocrit (%)	<24	5/221	2.3	3/116	2.6	7/230	3.0	4/121	3.3
Hemoglobin (g/dL)	<8	6/221	2.7	1/116	0.9	9/230	3.9	3/121	2.5
Platelet count (cells/μL)	<75,000	1/220	0.5	2/116	1.7	3/230	1.3	3/121	2.5
	<50,000	0/220	0.0	1/116	0.0	1/230	0.4	3/121	1.7
Serum alkaline phosphatase (U/L)	>2.5 x ULN	6/206	2.9	1/103	1.0	6/217	2.8	1/110	0.9
	>5 x ULN	0/206	0.0	0/103	0.0	0/217	0.0	0/110	0.0
Serum creatinine (mg/dL)	>1.5 x ULN	2/220	0.9	4/115	3.5	2/230	0.9	4/121	3.3
	>3 x ULN	0/220	0.0	0/115	0.0	0/230	0.0	0/121	0.0
Total serum bilirubin (mg/dL)	>1.5 x ULN	6/208	2.9	2/104	1.9	7/221	3.2	3/110	2.7
	>2.5 x ULN	4/208	1.9	1/104	1.0	5/221	2.3	2/110	1.8

N = The total number of patients in treatment group.
n/m = Number of patients with CSLA/number of patients with laboratory test at baseline and postbaseline.

(Modified Applicant's Tables 94 and 97, Volume 17 of 22, pages 248 and 2252)

Rash

Rash occurred in 6 patients in the MK-0826 group and in 1 patient in the ceftriaxone group during study therapy or the 14-day follow-up period. These numbers included patients with urticaria. Of the rashes reported, 2 in the MK-0826 group and none in the ceftriaxone group were considered drug-related. No cases of rash causing discontinuation of the study drug were reported in either treatment group.

Medical Officer's Comment: ***The seizure that occurred in the patient on MK-0826 parenteral therapy may represent a real signal in the database, given the known association of seizures with carbapenem antimicrobials. This issue will be addressed in more detail in the Integrated Summary of Safety.***

There appeared to be a greater percentage of patients that developed absolute neutrophils counts <1800 in the MK-0826 group. This issue will be further addressed in the Integrated Summary of Safety.

Taking into account the 2:1 randomization schedule used in this study, the overall rates of liver function abnormalities and rash were comparable between the two treatment groups.

7.1.3.3.9 Conclusions

In adult patients with serious community-acquired pneumonia (CAP) treated for up to 14 days with parenteral administration of MK-0826 1 g per day, with an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions regarding safety and tolerability can be drawn:

1. The safety profile of MK-0826 was similar to ceftriaxone 1 g daily based on the overall safety profile including the frequency of drug-related serious adverse experiences (with the possible exceptions of seizure and absolute neutrophil count <1800 cells/*u*L), discontinuations due to drug-related adverse experiences, and the assessment of infusion-related local tolerability in patients with CAP.
2. The seizures reported for AN 3843, in the MK-0826 group, are notable and strongly suggestive of a dose dependent drug-related adverse event.
3. The finding of a greater percentage of patients that developed decreased neutrophil counts (<1800 cells/uL) in the MK-0826 group is consistent with toxicity predicted by preclinical data.
4. The tolerability at the IV infusion site for MK-0826 was similar to that of ceftriaxone.
5. A total of nine patients in the MK-0826 group were treated with IM therapy and no local reactions were reported in any of these nine patients.

7.1.3.4 Indication Safety and Tolerability Conclusion

Based on the data provided for studies 018 and 020, in adult patients with serious community-acquired pneumonia (CAP) treated for up to 14 days with parenteral administration of MK-0826 1 g per day, with an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions regarding safety and tolerability can be drawn:

1. The safety profile of MK-0826 was similar to ceftriaxone 1 g daily based on the overall safety profile including the frequency of drug-related serious adverse experiences (with the possible exceptions of seizure and absolute neutrophil count <1800 cells/*u*L), discontinuations due to drug-related adverse experiences, and the assessment of infusion-related local tolerability in patients with CAP.
2. The seizures reported for AN 7057 (Protocol 018) and AN 3843 (Protocol 020), in the MK-0826 groups, are notable and are consistent with drug-related seizures that are known to occur in association with other members of the carbapenem class of antimicrobials.
3. The finding of a greater percentage of patients that developed decreased neutrophil counts (<1800 cells/uL) in the MK-0826 group, in Protocol 020, is consistent with toxicity predicted for MK-0826 by preclinical data.
4. Liver enzyme elevations and the incidence of rash (and related skin adverse events) were similar in the MK-0826 groups and the ceftriaxone groups.
5. The tolerability at the IV infusion site for MK-0826 was similar to that of ceftriaxone.
6. A total of nine patients in the MK-0826 group were treated with IM therapy in Protocol 020 and no local reactions were reported in any of these nine patients.

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7.1.4 CSSSI

Please see review by Dr. Janice Pohlman. (This review has been entered separately into DFS.)

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7.1.5 cUTI

Please see review by Dr. Thomas Smith. (This review has been entered separately into DFS.)

7.2 Overall Integrated Summary of Safety

7.2.1 Reviewer:

Jean M. Mulinde
Medical Officer, HFD-520

Review Dates

Received by Reviewer:	December 5, 2000
Review Begun:	February 20, 2001
Review Completed:	October 3, 2001
Revised:	October 23,2001

7.2.2 Material Reviewed

The following submissions were reviewed by the Medical Officer to construct the Integrated Review of Safety for ertapenem:

November 30, 2000	(Original NDA 21,337 submission)
January 10, 2001	(Revised data sets for clinical and laboratory adverse events)
March 22, 2001	(Preliminary, unaudited, summary results of Protocol 029)
March 30, 2001	(4 month safety update)
June 22, 2001	(Requested additional information on patients experiencing arrythmias)
July 3, 2001	(Final study report for Protocol 029-IM safety and tolerability study)
July 17, 2001	(Requested CRFs)
July 18, 2001	(Requested CRF)
July 29, 2001	(Requested CRFs)
July 30, 2001	(Requested CRFs)
August 22, 2001	(Corrected ISS tables)
August 24, 2001	(Further analyses of deaths occurring in clinical studies)
August 30, 2001	(New data set containing ECG information and explanation to QT/QTc measurements in Phase I studies)
September 14, 2001	(Updated ISS tables inclusive of patients in protocol 029, Part I)
September 21, 2001	(Updated ISS tables inclusive of patients in protocol 029, Part II)

7.2.3 Extent of Exposure

Phase I Studies

The Applicant presented safety data from eleven Phase I studies that enrolled 252 healthy subjects (206 subjects that received ertapenem, 14 subjects that received ertapenem with probenecid, and 32 subjects that received placebo). A summary of the Phase I clinical pharmacology studies is displayed in the following table.

Summary of Ertapenem Clinical Pharmacology Studies

Protocol	Study Description	Total Number of Subjects Enrolled (N=252)	Total Number of Subjects Dosed With Ertapenem[1] (N=220)	Placebo (N=32)	Duration of Drug Administration (Days)
001	Single/multiple rising dose	66	50	16	1 to 15
009	Dose proportionality	16	16	0	4
010	Pharmacokinetics in elderly	15	15	0	1 and 7
011	Pilot intramuscular administration	11	9	2	2
012	Radiolabelled disposition	7	7	0	1
013	14-day intravenous safety	24	20	4	14
015	Pharmacokinetics in renal insufficiency	26	26	0	1 to 2
019	Intramuscular/intravenous administration comparison	26	22	4	10
026	Levels in skin blister fluid	13	13	0	3
027	Effect of probenecid	14	14	0	2
030	Multiple-dose intramuscular safety	34	28	6	3

[1] Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).

(Applicant's Table E-1, Volume 2 of 22, page E-17)

The following table displays the duration of treatment with ertapenem for all subjects in the Phase I studies categorized by dose levels. (Most subjects who received doses of <1 g, 1.5 g, 2 g, or 3 g participated in studies in which they received 1 or more additional dose levels and, thus, individual subjects contribute to the total subject number for more than 1 dose level, but are only counted once within a dose level.)

Duration of Ertapenem Treatment by Daily Dose for Phase I Studies

Treatment Group	Total Subjects	Days of Treatment				Total Subject-Days on Ertapenem	Range of Duration on Ertapenem (Days)	Mean Duration on Ertapenem (Days)
		1	2 to 7	8 to 14	15			
Ertapenem [1]:								
Intravenous:								
Total subjects on <1 g	41	19	10	12	0	135	1 to 8	3.3
Total subjects on 1 g	149	55	73	15	6	589	1 to 15	4.0
Total subjects on 1.5 g	6	6	0	0	0	6	1 to 1	1.0
Total subjects on 2 g	42	36	0	6	0	84	1 to 8	2.0
Total subjects on 3 g	29	23	0	6	0	71	1 to 8	2.4
Intramuscular:								
Total subjects on <1 g	9	9	0	0	0	9	1 to 1	1.0
Total subjects on 1 g	57	12	28	17	0	235	1 to 8	4.1

[1] Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).

Note: The table displays the number of subjects receiving each daily dose. A subject may be counted multiple times if, during the course of the study, the subject's daily dosage changed.

(Applicant's Table E-3, Volume 2 of 22, page E-35)

Phase II and III Studies

The mean number of days on all study therapy (parenteral study therapy and permitted oral antimicrobial therapy) was 8.9 in the 1 gm ertapenem group, 8.4 in the 1.5 gm ertapenem group, 9.3 in the 2 gm ertapenem group, 7.4 in the

piperacillin/tazobactam group, and 10.7 in the ceftriaxone group. The mean number of days on parenteral therapy (IV or IM) was 5.4 in the 1 gm ertapenem group, 6.1 in the 1.5 gm ertapenem group, 3.8 in the 2 gm ertapenem group, 4.6 in the ceftriaxone group, and 7.4 in the piperacillin/tazobactam group. The piperacillin/tazobactam group does not include an oral therapy option, therefore, the mean number of days on study therapy and parenteral therapy are the same. One hundred eleven patients in the 1 gm ertapenem group received IM therapy with a mean of 3.9 days (range 1 to 7 days) and 42 patients in the ceftriaxone group received IM therapy with a mean of 4.0 days (range 2 to 9 days).

The proportion of patients who used oral antimicrobial therapy was 928/1954 (47.5%) in the ertapenem 1 gm group, 24/64 (37.5%) in the ertapenem 1.5 gm group, 27/30 (90%) in the ertapenem 2 gm group, 0/775 (0%) in the piperacillin/tazobactam group, and 759/942 (80.6%) in the ceftriaxone group. These proportions reflect the permitted use of oral antimicrobial follow-up only in those studies that used ceftriaxone as a comparator. Studies that used piperacillin/tazobactam as a comparator had no oral therapy option. The mean duration of oral antimicrobial therapy was 7.4 days overall and the range of duration of oral antimicrobial therapy across all treatment groups that used the oral switch option was 1 to 22 days.

In order to determine the number of days that study therapy was missed, the Applicant assumed that the number of days from the first to the last dose of study therapy (pertaining only to parenteral study therapy, not to oral therapy) was the duration of therapy intended by the investigator. The last day of study therapy was considered the day on which the patient received the last blinded dose of study therapy, whether the study therapy or placebo therapy was received. A calendar day in which a patient received no active study therapy was counted as a day of missed study therapy. If the patient received only a placebo dose on the last day of study therapy (a situation that occurred in 235 patients in the ertapenem 1 gm group), then this day was counted as a day in which the patient missed study therapy. This situation generally pertained only to the ertapenem 1 gm treatment group in studies where the comparator was piperacillin/tazobactam (Protocols 016, 017, and 023), for which the last 3 doses of each 24-hour period were placebos. Although it appears that 291 patients in the ertapenem 1 gm group missed a day of study therapy, 235 patients who actually received the full duration of therapy were included in this count because they received only placebo doses on the last calendar day of study therapy. Therefore, only 56 patients in the ertapenem 1 gm group actually missed one or more days of study therapy during their intended study therapy duration.

The following table displays the extent of exposure to all study drugs (includes parenteral, IV and/or IM, as well as optional oral therapy) by treatment group for all patients who received at least 1 dose of therapy.

Extent of Exposure by Dose and Treatment Group
(Treated Population)

	Ertapenem 1 g (N=1954)[1]	Ertapenem 1.5 g (N=64)	Ertapenem 2 g (N=30)	P/T (N=774)[2]	CTX (N=942)[3]	Total (N=3764)
Days on Study Therapy						
n	1954	64	30	774	942	3764
Mean	8.9	8.4	9.3	7.4	10.7	9.0
SD	4.3	4.8	3.3	3.5	4.9	4.2
Median	10.0	7.0	8.0	6.0	11.0	10.0
Range						
Days on Parenteral Therapy						
n	1954	64	30	774	942	3764
Mean	5.4	6.1	5.8	5.4	4.6	5.6
SD	3.2	3.6	1.3	3.5	2.5	3.2
Median	5.0	5.0	5.0	6.0	4.0	5.0
Range						
Days on IV Therapy						
n	1867	64	30	774	912	3647
Mean	5.4	6.1	5.8	5.4	4.6	5.6
SD	3.2	3.6	1.3	3.5	2.6	3.3
Median	5.0	5.0	5.0	6.0	4.0	5.0
Range						
Days on IM Therapy						
n	111	--	--	--	42	153
Mean	3.9	--	--	--	4.0	3.9
SD	2.0	--	--	--	1.6	1.9
Median	4.0	--	--	--	4.0	4.0
Range						
Days on Oral Therapy[4]						
n	928	34	27	--	799	3788
Mean	7.4	6.0	6.1	--	7.5	7.4
SD	2.7	2.8	2.6	--	2.6	2.7
Median	7.0	6.5	5.0	--	7.0	7.0
Range						
Days Missed Therapy						
n	291[5]	22	--	--	31	344
Mean	1.1	1.0	--	--	1.8	1.2
SD	0.7	0.2	--	--	2.8	1.0
Median	1.0	1.0	--	--	1.0	1.0
Range						

[1] Includes patients with renal dose adjustments (0.5 g daily for ertapenem 1 g, and according to the manufacturers label for P/T).
[2] Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1 g group and 5 patients in the ceftriaxone group).
[3] Included patients who also received metronidazole.
[4] Oral therapy was generally amoxicillin-clavulanate or ciprofloxacin depending on underlying infection.
[5] Includes 235 patients who did not actually receive any days of study therapy, but are counted in the total because all study subjects on the last calendar day were placebo.
[6] One patient (Protocol 014; AN 28881, after discontinuation of IV study therapy on Day 6, appears in the database to have missed 7 days of therapy when actually the patient was a treatment failure or discontinued as of IV therapy.

P/T = Piperacillin/tazobactam.
CTX = Ceftriaxone any dose.
N = Number of patients in each treatment group.
n = Number of patients in category.
SD = Standard deviation.
IV = Intravenous.
IM = Intramuscular.

(Table E-15, September 14, 2001 submission)

Medical Officer's Comment: ***For P/T the mean and median days of parenteral therapy appear greater than the mean and median days of parenteral therapy for ertapenem 1 gm, and for ceftriaxone the mean and median days of parenteral therapy appear less than the mean and median days of parenteral therapy for ertapenem 1 gm. However, the ertapenem 1 gm group is comprised of both patients enrolled in studies that allowed parenteral therapy only (comparator, pipercillin/tazobactam) and studies that allowed a switch to oral therapy (comparator, ceftriaxone). When studies that allowed only parenteral therapy and studies that allowed switch to oral therapy are viewed separately, the extent of exposure appears similar between ertapenem and the respective comparator agent.***

The following table displays the extent of exposure to parenteral ertapenem therapy by dose and duration for all patients who received at least 1 dose of study therapy in all clinical studies. Any ertapenem dose actually received, irrespective of treatment group, whether a result of a one time dose shift as permitted by protocol, administration of a fifth dose on a 6-hourly administration schedule,

dose reduction for renal insufficiency, dose increase from 1 to 2 g, or even doses given in error in patients randomized to one of the comparator groups is displayed.

Extent of Exposure by Dose and Duration of Ertapenem Therapy
(Treated Population)

Ertapenem	Number of Days on Parenteral Therapy								
	≤3	4 to 7	8 to 10	11 to 14	≥15	Total Patients	Range	Total Days	Mean
ANY DOSE	670	1011	208	138	22	2049[a]	[redacted]	10962	5.3
0.5 g	8	3	0	1	0	12	[redacted]	41	3.4
1 g	656	938	199	128	20	1941	[redacted]	10254	5.3
1.5 g	15	34	5	10	0	64	[redacted]	392	6.1
2 g	138	19	0	0	0	157	[redacted]	271	1.7
3 g	2[b]	0	0	0	0	2	[redacted]	2	1.0
3.1 to 4.0 g	2[c]	0	0	0	0	2	[redacted]	2	1.0

Note: The table displays the number of patients receiving each daily dose. A patient may be counted multiple times if, during the course of the study, the patient's daily dosage changed.

[a] Includes 2 patients in comparator groups that inadvertently received 1 or more doses of ertapenem.

[b] Includes 1 patient who received 3 g for 1 day. Also, includes 1 patient who received two 1.5-g doses in 1 day.

[c] Includes 1 patient who received ertapenem 1 g for 9 days. One of these doses was inadvertently entered in the database as 3.375 g. Also includes 1 patient who received 4 g on 1 day.

(Table E-16, September 14, 2001 submission)

Medical Officer's Comment: ***The large number of patients that appear to have received ertapenem 2 gms for ≤3 days is accounted for primarily by the one time dose shift permitted in all the protocols and the inclusion of a fifth 6-hourly dose in a calendar day that occasionally occurred in those protocols with a 6-hourly dosing regimen for the comparator (Protocols 016, 017, and 023). While a dose adjustment to 2 gm was allowed for patients with documented PRSP with inadequate clinical response in Protocols 018 and 020, none of the patients in whom this dose adjustment was actually used met this criterion and the five ertapenem patients that received this adjustment did so as protocol violations.***

7.2.4 Demographics

Phase I Studies

The baseline characteristics of subjects in the Phase I studies are displayed in the following table.

Baseline Subject Characteristics by Treatment Group for Phase I Studies

	Ertapenem† (N=220)	Placebo (N=32)	Total (N=252)
	n (%)	n (%)	n (%)
Gender			
Male	141 (64.1)	22 (68.8)	163 (64.7)
Female	79 (35.9)	10 (31.3)	89 (35.3)
Age (Years)			
18 to 25	50	12	62
26 to 40	101	13	114
41 to 64	38	3	41
65 to 74	22	3	25
>74	9	1	10
Mean	38.4	34.8	37.9
SD	16.7	16.7	16.7
Median	33.0	31.0	33.0
Range	18 to 82	18 to 77	18 to 82
Race			
Asian	5 (2.3)	1 (3.1)	6 (2.4)
Black	39 (17.7)	6 (18.8)	45 (17.9)
Caucasian	138 (62.7)	19 (59.4)	157 (62.3)
Hispanic	8 (3.6)	0 (0.0)	8 (3.2)
Hispanic/Black	1 (0.5)	0 (0.0)	1 (0.4)
Native American	1 (0.5)	0 (0.0)	1 (0.4)
Spanish	1 (0.5)	0 (0.0)	1 (0.4)
White	27 (12.3)	6 (18.8)	33 (13.1)

† Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).

(Applicant's Table E-4, Volume 2 of 22, page E-36)

Medical Officer's Comment: ***The majority of subjects in the Phase I studies were male (64.7%); while not evenly distributed by gender, women have been relatively well represented. The majority of subjects in the Phase I studies were of "caucasian" or "white" (75.4%) or "black" (17.9%) race. Therefore safety information from these studies as it pertains to other races is limited.***

Phase II and III Studies

The following table displays the baseline characteristics of all treated patients in the clinical studies.

Baseline Patient Characteristics by Disease and Treatment Group in All Clinical Studies

	Ertapenem 1 gm (N=1954)[2]	Ertapenem 1.5 gm (N=64)	Ertapenem 2 gm (N=30)	P/T (N=774)[1]	CTX (N=942)[2]	Total (N=3764)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender						
Male	909 (46.5)	42 (65.6)	17 (56.7)	368 (47.5)	461 (48.9)	1797 (47.7)
Female	1045 (53.5)	22 (34.4)	13 (43.3)	406 (52.5)	481 (51.1)	1967 (52.3)
Race						
Black	254 (13.0)	7 (10.9)	15 (50.0)	109 (14.1)	100 (10.6)	485 (12.9)
Caucasian	1029 (52.7)	38 (59.4)	10 (33.3)	366 (47.3)	558 (59.2)	2001 (53.2)
Hispanic	472 (24.2)	13 (20.3)	4 (13.3)	217 (28.0)	182 (19.3)	888 (23.6)
Mestizo	109 (5.6)	0 (0.0)	0 (0.0)	50 (6.5)	53 (5.6)	212 (5.6)
Other	90 (4.6)	6 (9.4)	1 (3.3)	32 (4.1)	49 (5.2)	178 (4.7)
Age (Years)						
< 18	19	0	0	15	4	38
18–40	781	25	13	397	282	1498
41-64	652	21	10	227	332	1242
65-74	267	11	6	80	165	529
≥ 75	235	7	1	55	159	457
Mean	48.0	48.7	47.3	42.3	53.1	48.1
S.D.	20.3	19.1	17.6	18.9	20.0	20.2
Median	46.0	49.0	45.5	38.0	54.0	46.0
Range	15 to 99	19 to 79	20 to 77	16 to 92	15 to 98	15 to 99
Index Infection						
Urinary Tract Infection	487	0	0	0	386	873
Severe[4]	201 (41.3)	0	0	0	147 (38.1)	348 (39.9)
Skin and Skin Infections	286	0	0	258	11	555
Severe[4]	49 (17.1)	0	0	44 (17.1)	0	93 (16.8)
Community-Acquired Pneumonia	506	0	30	0	406	942
Severe[4]	122 (24.1)	0	0	0	110 (27.1)	232 (24.6)
Intra-abdominal Infections	373	64	0	325	109	871
Severe[4]	26 (7.0)	7 (10.9)	0	21 (6.5)	4 (3.7)	58 (6.7)
Pelvic Infections	215	0	0	191	0	406
Severe[4]	60 (27.9)	0	0	47 (24.6)	0	107 (26.4)
Intramuscular Safety Study (Protocol 029)[5]	87	0	0	0	30	117
Timing of Enrollment With Respect to Enhanced Blinding Procedures[3]						
Before	689 (36.9)	64 (100)	30 (100)	332 (42.8)	388 (42.5)	1503 (41.2)
After	1177 (63.1)	0 (0.0)	0 (0.0)	443 (57.2)	524 (57.5)	2144 (58.8)

[1] Includes patients with renal dose adjustments (0.5- g dose for ertapenem 1 g and according to the manufacturers label for P/T).
[2] Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1- g group and 5 patients in the ceftriaxone group).
[3] Includes patients who also received metronidazole.
[4] Patients are graded as severe if they met the criteria for severe index infection as defined within the individual protocol. The proportion of patients with severe infection is the number of patients with severe index infection/ total number of patients with the index infection.
[5] Patients were not graded for severity of infection.
[6] Only includes patients from studies using intravenous study therapy. Patients from the intramuscular safety study (Protocol 029) are excluded.
P/T = Piperacillin/ tazobactam.
CTX = Ceftriaxone.

(Table E-17, September 14, 2001 submission)

Medical Officer's Comment: *Male and female patients were approximately equally represented in the safety database with a similar distribution of gender between the ertapenem 1 gm and comparator groups. Black, Caucasian, and Hispanic patients were well represented in the safety database, but limited information regarding the safety and tolerability of ertapenem in patients of other races is available.*

The mean and median ages of patients appear greater in the ceftriaxone group and less in the piperacillin/tazobactam group than the mean and median ages of patients in the ertapenem 1 gm group. The MO believes this difference is a reflection of different age demographics that are expected to occur in different indications. The data presented by the Applicant reflect the combining of all patients that received ertapenem 1 gm across all studies, both patients enrolled in studies that allowed parenteral therapy only (comparator, pipercillin/tazobactam) and studies that allowed a switch to oral therapy (comparator, ceftriaxone). When studies that allowed only parenteral therapy and studies that allowed switch to oral therapy are viewed separately, the mean and median ages of patients appear similar between the ertapenem 1 gm group and the appropriate comparator group (pipercillin/tazobactam or ceftriaxone).

The distribution of disease severity, as defined in the individual protocols, was generally similar among treatment groups.

The MO reviewed the number of patients with specific secondary diagnoses at baseline (Applicant's Reference 63, clinstat/other/0063.pdf) in the Phase II and III studies, and secondary diagnoses were distributed approximately evenly between the ertapenem 1 gm group and the combined comparator group (patients receiving pipercillin/tazobactam or ceftriaxone).

The MO also reviewed the number of patients with specific prior therapies (Applicant's Reference 64, clinstat/other/0064.pdf) in the Phase II and III studies and found that specific prior therapies were distributed approximately evenly between the ertapenem 1 gm group and the combined comparator group (patients receiving pipercillin/tazobactam or ceftriaxone). Concomitant therapies (Applicant's Reference 65, clinstat/other/0065.pdf) were also were distributed approximately evenly between the ertapenem 1 gm group and the combined comparator group (patients receiving pipercillin/tazobactam or ceftriaxone).

7.2.5 Treatment Emergent Adverse Events

Phase I Studies

Clinical adverse experiences occurred in 62.3% of subjects that received ertapenem and 34.4% of subjects that received placebo. The following table displays the number (%) of subjects in the Phase I studies with any clinical adverse experience.

Clinical Adverse Experience Summary by Treatment Group for Phase I Studies

Number (%) of subjects	Ertapenem† (N=220)		Placebo (N=32)	
	n	(%)	n	(%)
with one or more adverse experiences	137‡	(62.3)	11	(34.4)
with no adverse experience	83	(37.7)	21	(65.6)
with drug-related adverse experiences §	88	(40.0)	5	(15.6)
with serious adverse experiences	0	(0.0)	0	(0.0)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	11	(5.0)	0	(0.0)
discontinued due to a drug-related adverse experience	10	(4.5)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)

† Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).
‡ Includes one subject (AN 0003 of Protocol 027) who experienced one adverse experience while receiving probenecid alone.
§ Determined by the investigator to be possibly, probably, or definitely drug related.

(Applicant's Table E-5, Volume 2 of 22, page E-37)

The number (%) of subjects in the Phase I studies with clinical adverse experiences (incidence > 0% in either treatment group) by body system is displayed in the following table.

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	MK-0826 (N=220)			Placebo (N=32)		
	n	(%)	[DR]	n	(%)	[DR]
Subjects with one or more adverse experiences	136	(61.8)	[88]	11	(34.4)	[5]
Subjects with no adverse experience	84	(38.2)		21	(65.6)	
Body as a Whole/Site Unspecified	**39**	**(17.7)**	**[28]**	**4**	**(12.5)**	**[3]**
Asthenia/fatigue	5	(2.3)	[3]	0	(0.0)	[0]
Cold sensation	1	(0.5)	[0]	0	(0.0)	[0]
Ecchymosis, injection site	3	(1.4)	[3]	1	(3.1)	[0]
Edema/swelling	2	(0.9)	[0]	0	(0.0)	[0]
Erythema, catheter site	1	(0.5)	[0]	0	(0.0)	[0]
Erythema, injection site	6	(2.7)	[6]	1	(3.1)	[1]
Fever	4	(1.8)	[2]	0	(0.0)	[0]
Flu-like illness	1	(0.5)	[0]	0	(0.0)	[0]
Inflammation, injection site	1	(0.5)	[1]	0	(0.0)	[0]
Malaise	1	(0.5)	[1]	0	(0.0)	[0]
Orthostatic effects	2	(0.9)	[2]	0	(0.0)	[0]
Pain/tenderness/soreness, injection site	3	(1.4)	[2]	2	(6.3)	[1]
Pain, abdominal	11	(5.0)	[8]	1	(3.1)	[1]
Pain, chest	2	(0.9)	[0]	0	(0.0)	[0]
Pain, pelvic	1	(0.5)	[0]	0	(0.0)	[0]
Pruritus, injection site	2	(0.9)	[2]	0	(0.0)	[0]
Swelling, injection site	2	(0.9)	[2]	1	(3.1)	[1]
Trauma	0	(0.0)	[0]	1	(3.1)	[0]
Warm sensation	1	(0.5)	[1]	0	(0.0)	[0]
Cardiovascular System	**11**	**(5.0)**	**[4]**	**0**	**(0.0)**	**[0]**
Extravasation	1	(0.5)	[0]	0	(0.0)	[0]
Hematoma	1	(0.5)	[0]	0	(0.0)	[0]
Hypotension	1	(0.5)	[0]	0	(0.0)	[0]
Hypotension, orthostatic	2	(0.9)	[2]	0	(0.0)	[0]
Infused vein complication	4	(1.8)	[2]	0	(0.0)	[0]
Occlusion, vascular graft	1	(0.5)	[0]	0	(0.0)	[0]
Phlebitis/thrombophlebitis	1	(0.5)	[0]	0	(0.0)	[0]
Tachycardia	1	(0.5)	[0]	0	(0.0)	[0]
Digestive System	**85**	**(38.6)**	**[62]**	**6**	**(18.8)**	**[4]**
Acid regurgitation	5	(2.3)	[0]	0	(0.0)	[0]
Anorexia	2	(0.9)	[2]	0	(0.0)	[0]
Constipation	3	(1.4)	[2]	0	(0.0)	[0]

Diarrhea	52	(23.6)	[41]	3	(9.4)	[2]
Dry mouth	4	(1.8)	[1]	1	(3.1)	[0]
Dyspepsia	7	(3.2)	[2]	1	(3.1)	[0]
Fecal abnormality	4	(1.8)	[3]	1	(3.1)	[1]
Flatulence	1	(0.5)	[1]	1	(3.1)	[1]
Hepatomegaly	1	(0.5)	[0]	0	(0.0)	[0]
Lip abnormality	1	(0.5)	[0]	0	(0.0)	[0]
Nausea	35	(15.9)	[28]	2	(6.3)	[2]
Pain, dental	1	(0.5)	[0]	0	(0.0)	[0]
Reflux esophagitis	1	(0.5)	[1]	0	(0.0)	[0]
Thirst	1	(0.5)	[0]	0	(0.0)	[0]
Vomiting	10	(4.5)	[7]	1	(3.1)	[1]
Metabolic, Nutritional, Immune	**3**	**(1.4)**	**[1]**	**0**	**(0.0)**	**[0]**
Allergy, animal	1	(0.5)	[0]	0	(0.0)	[0]
Allergy, non-drug	1	(0.5)	[0]	0	(0.0)	[0]
Weight loss	1	(0.5)	[1]	0	(0.0)	[0]
Musculoskeletal System	**20**	**(9.1)**	**[4]**	**1**	**(3.1)**	**[0]**
Heaviness, regional	2	(0.9)	[1]	0	(0.0)	[0]
Myalgia	3	(1.4)	[2]	0	(0.0)	[0]
Pain, arm	2	(0.9)	[0]	0	(0.0)	[0]
Pain, back	4	(1.8)	[0]	0	(0.0)	[0]
Pain, foot	1	(0.5)	[0]	0	(0.0)	[0]
Pain, hip	1	(0.5)	[0]	0	(0.0)	[0]
Pain, leg	3	(1.4)	[1]	0	(0.0)	[0]
Pain, musculoskeletal	2	(0.9)	[0]	1	(3.1)	[0]
Pain, neck	2	(0.9)	[0]	0	(0.0)	[0]
Stiffness	1	(0.5)	[0]	0	(0.0)	[0]
Weakness, muscle	1	(0.5)	[0]	0	(0.0)	[0]
Nervous System and Psychiatric Disorder	**68**	**(30.9)**	**[34]**	**5**	**(15.6)**	**[3]**
Anxiety	1	(0.5)	[1]	0	(0.0)	[0]
Depression	2	(0.9)	[0]	0	(0.0)	[0]
Dizziness	17	(7.7)	[10]	2	(6.3)	[2]
Headache	49	(22.3)	[28]	3	(9.4)	[1]
Hypesthesia	1	(0.5)	[0]	0	(0.0)	[0]
Mental acuity decreased	1	(0.5)	[0]	0	(0.0)	[0]
Paresthesia	1	(0.5)	[1]	0	(0.0)	[0]
Somnolence	15	(6.8)	[4]	0	(0.0)	[0]
Respiratory System	**23**	**(10.5)**	**[2]**	**4**	**(12.5)**	**[0]**
Bronchitis	2	(0.9)	[0]	0	(0.0)	[0]
Congestion, nasal	5	(2.3)	[1]	1	(3.1)	[0]
Cough	1	(0.5)	[0]	0	(0.0)	[0]

Discomfort, pharyngeal	1	(0.5)	[1]	0	(0.0)	[0]
Epistaxis	2	(0.9)	[0]	0	(0.0)	[0]
Hoarseness	1	(0.5)	[0]	0	(0.0)	[0]
Infection, respiratory, upper	9	(4.1)	[0]	2	(6.3)	[0]
Pharyngitis	5	(2.3)	[1]	0	(0.0)	[0]
Rhinorrhea	1	(0.5)	[0]	1	(3.1)	[0]
Skin and Skin Appendage	**20**	**(9.1)**	**[9]**	**2**	**(6.3)**	**[0]**
Ecchymosis	2	(0.9)	[0]	1	(3.1)	[0]
Eczema	0	(0.0)	[0]	1	(3.1)	[0]
Erythema	3	(1.4)	[1]	0	(0.0)	[0]
Excoriation	1	(0.5)	[0]	0	(0.0)	[0]
Folliculitis	1	(0.5)	[1]	0	(0.0)	[0]
Laceration	1	(0.5)	[0]	0	(0.0)	[0]
Pruritus	2	(0.9)	[1]	0	(0.0)	[0]
Rash	5	(2.3)	[3]	0	(0.0)	[0]
Sweating	3	(1.4)	[2]	0	(0.0)	[0]
Urticaria	2	(0.9)	[1]	0	(0.0)	[0]
Special Senses	**10**	**(4.5)**	**[4]**	**2**	**(6.3)**	**[0]**
Blurred vision	1	(0.5)	[0]	0	(0.0)	[0]
Dry eyes	0	(0.0)	[0]	1	(3.1)	[0]
Itching, eye	1	(0.5)	[1]	0	(0.0)	[0]
Neuronitis, vestibular	1	(0.5)	[0]	0	(0.0)	[0]
Otitis	1	(0.5)	[0]	0	(0.0)	[0]
Pain, ear	1	(0.5)	[0]	0	(0.0)	[0]
Pain, eye	0	(0.0)	[0]	1	(3.1)	[0]
Perversion, taste	3	(1.4)	[3]	1	(3.1)	[0]
Swelling, eye	0	(0.0)	[0]	1	(3.1)	[0]
Tearing	1	(0.5)	[0]	0	(0.0)	[0]
Tinnitus	1	(0.5)	[0]	0	(0.0)	[0]
Urogenital System	**12**	**(5.5)**	**[3]**	**1**	**(3.1)**	**[0]**
Hot flashes	4	(1.8)	[1]	0	(0.0)	[0]
Menstruation disorder	3	(1.4)	[0]	1	(3.1)	[0]
Pain, vaginal	1	(0.5)	[0]	0	(0.0)	[0]
Pruritus, vaginal	2	(0.9)	[1]	0	(0.0)	[0]
Urinary frequency	1	(0.5)	[0]	0	(0.0)	[0]
Vaginitis	2	(0.9)	[2]	0	(0.0)	[0]

n: Number of subjects reporting clinical adverse experiences.

[DR]: Number of subjects reporting clinical adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.

Although a subject may have had two or more adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

All body systems are listed in which at least 1 subject had an adverse experience.

(Applicant's Reference 76, clinstat/other/0076.pdf)

Medical Officer's Comment: *The body systems in which clinical adverse experiences occurred most commonly for the ertapenem group were digestive, nervous/ psychiatric, and body as a whole/site unspecified and for the placebo group were digestive and nervous/ psychiatric. The specific adverse experiences that occurred most commonly in the ertapenem group were diarrhea (23.6%), headache (22.3%), nausea (15.9%), dizziness (7.7%), somnolence (6.8%), and abdominal pain (5.0%). The specific adverse experiences that occurred most commonly in the placebo group were diarrhea (9.4%), headache (9.4%), pain/sore/tenderness at the injection site (6.3%), nausea (6.3%), dizziness (6.3%), and upper respiratory infection (6.3%). The drug-related specific clinical adverse experiences that occurred most commonly in the ertapenem group were diarrhea (18.6%), headache (12.7%), and nausea (12.7%). The drug-related specific clinical adverse experiences that occurred most commonly in the placebo group were diarrhea (6.3%), nausea (6.3%), and dizziness (6.3%).*

Examining the most common adverse experiences, the incidence of nausea, diarrhea, somnolence, headache, and vomiting may have been dose related. The following table displays the number of subjects who received ertapenem at various dose levels with clinical adverse experiences (incidence ≥3% at any dosage level).

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Number (%) of Subjects at Dose With Specific Clinical Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by Body System and Dose (Ertapenem) in Phase I Studies—Total and Drug Related

	Ertapenem														
	<1 g (N=50)			1 g (N=187)			1.5g (N=6)			2g (N=42)			3g (N=29)		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Subjects with one or more adverse experiences	28	(56.0)	14	107	(57.2)	70	3	(50.0)	3	27	(64.3)	15	23	(79.3)	20
Subjects with no adverse experience	22	(44.0)		80	(42.8)		3	(50.0)		15	(35.7)		6	(20.7)	
Body as a Whole/Site Unspecified	2	(4.0)	1	33	(17.6)	23	0	(0.0)	0	4	(9.5)	3	4	(13.8)	3
Erythema, injection site	0	(0.0)	0	6	(3.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Fever	1	(2.0)	0	3	(1.6)	2	0	(0.0)	0	0	(0.0)	0	1	(3.4)	1
Flu-like illness	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	0
Orthostatic effects	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(4.8)	2	0	(0.0)	0
Pain, abdominal	0	(0.0)	0	10	(5.3)	7	0	(0.0)	0	0	(0.0)	0	2	(6.9)	2
Cardiovascular System	1	(2.0)	0	9	(4.8)	3	0	(0.0)	0	1	(2.4)	0	0	(0.0)	0
Digestive System	12	(24.0)	6	62	(33.2)	43	2	(33.3)	2	13	(31.0)	10	16	(55.2)	15
Acid regurgitation	0	(0.0)	0	2	(1.1)	0	0	(0.0)	0	3	(7.1)	0	0	(0.0)	0
Constipation	1	(2.0)	0	0	(0.0)	0	0	(0.0)	0	1	(2.4)	1	1	(3.4)	1
Diarrhea	9	(18.0)	5	34	(18.2)	26	2	(33.3)	2	4	(9.5)	4	10	(34.5)	9
Dyspepsia	0	(0.0)	0	7	(3.7)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Nausea	2	(4.0)	0	23	(12.3)	18	1	(16.7)	0	8	(19.0)	7	10	(34.5)	9
Vomiting	1	(2.0)	0	6	(3.2)	5	0	(0.0)	0	2	(4.8)	1	1	(3.4)	1
Metabolic, Nutritional, Immune	0	(0.0)	0	1	(0.5)	1	1	(16.7)	0	0	(0.0)	0	1	(3.4)	0
Allergy, animal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	0
Allergy, non-drug	0	(0.0)	0	0	(0.0)	0	1	(16.7)	0	0	(0.0)	0	0	(0.0)	0
Musculoskeletal System	2	(4.0)	0	15	(8.0)	3	0	(0.0)	0	2	(4.8)	0	1	(3.4)	1
Heaviness, regional	1	(2.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	1
Pain, neck	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(4.8)	0	0	(0.0)	0
Nervous System and Psychiatric Disorder	15	(30.0)	8	49	(26.2)	24	3	(50.0)	2	18	(42.9)	7	15	(51.7)	12
Depression	1	(2.0)	0	2	(1.1)	0	0	(0.0)	0	1	(2.4)	0	1	(3.4)	0
Dizziness	2	(4.0)	1	9	(4.8)	4	2	(33.3)	1	1	(2.4)	0	5	(17.2)	5
Headache	12	(24.0)	5	37	(19.8)	20	2	(33.3)	2	13	(31.0)	7	10	(34.5)	9
Paresthesia	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	1
Somnolence	2	(4.0)	0	8	(4.3)	2	0	(0.0)	0	7	(16.7)	1	2	(6.9)	1
Respiratory System	3	(6.0)	0	13	(7.0)	1	1	(16.7)	0	5	(11.9)	1	2	(6.9)	0
Bronchitis	1	(2.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	0
Congestion, nasal	1	(2.0)	0	2	(1.1)	0	1	(16.7)	0	1	(2.4)	1	0	(0.0)	0
Epistaxis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(4.8)	0	0	(0.0)	0
Infection, respiratory, upper	1	(2.0)	0	7	(3.7)	0	0	(0.0)	0	1	(2.4)	0	0	(0.0)	0
Pharyngitis	0	(0.0)	0	4	(2.1)	1	0	(0.0)	0	1	(2.4)	0	1	(3.4)	0

Number (%) of Subjects at Dose With Specific Clinical Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by Body System and Dose (Ertapenem) in Phase I Studies—Total and Drug Related

	Ertapenem[1]														
	<1 g (N=50)			1 g (N=187)			1.5g (N=6)			2g (N=42)			3g (N=29)		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Skin and Skin Appendage	2	(4.0)	1	14	(7.5)	6	0	(0.0)	0	2	(4.8)	0	2	(6.9)	2
Sweating	0	(0.0)	0	1	(0.5)	0	0	(0.0)	0	0	(0.0)	0	2	(6.9)	2
Special Senses	2	(4.0)	0	4	(2.1)	3	0	(0.0)	0	2	(4.8)	1	2	(6.9)	0
Neuronitis, vestibular	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	0
Pain, ear	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(3.4)	0
Urogenital System	0	(0.0)	0	10	(5.3)	2	0	(0.0)	0	1	(2.4)	0	1	(3.4)	1
Hot flashes	0	(0.0)	0	2	(1.1)	0	0	(0.0)	0	1	(2.4)	0	1	(3.4)	1

[1] Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).
N = Number of subjects treated with the designated dose of ertapenem.
n = Number of patients with a clinical adverse experience.
DR = Drug related; number of subjects reporting clinical adverse experiences determined by the investigator to be possibly, probably, or definitely drug related.
Although a subject may have had 2 or more adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
All body systems are listed in which at least 1 subject had an adverse experience.

(Applicant's Table E-7, Volume 2 of 22, pages E-43 to E-45)

Medical Officer's Comment: ***The incidence of diarrhea (10 to 35%) appeared to be higher at doses ≥1.5 gm than at doses ≤1 gm (18%). The diarrhea reported was mild to moderate in intensity.***

Nausea appeared more common at doses ≥1 gm as opposed to < 1 gm. This adverse event generally occurred in close temporal relationship with the ertapenem infusion suggesting that nausea may have been related in part, to the peak plasma concentration at the end of infusion. In the initial single-dose study, the 3 gm dose was initially infused over 1 hour, but, the infusion duration was changed to 2 hours due to the occurrence of nausea in 2 of 4 subjects at the 1 hour infusion rate. At the slower infusion rate, 8 of the 25 remaining subjects reported nausea at the 3 gm dose level. As one would expect, the incidence of vomiting appeared to reflect a similar dose-relationship to nausea; however, it occurred in too few subjects to establish the relationship definitively.

Somnolence occurred at a higher incidence in subjects who received the 2 gm (16.7%) and 3 gm (6.9%) doses than at lower doses (0 to 4.3%). This adverse experience was generally transient, mild to moderate in intensity, and judged not drug related by the investigator.

The incidence of headache (31 to 35%) appeared to be higher at doses ≥1.5 gm than at doses ≤1 gm (20 to 24%). Headaches were primarily mild to moderate in intensity.

Phase II and III Studies

This section presents safety information for the clinical studies (Protocols 002/008, 003, 004, 007, 014, 016, 017, 018, 020, 021, 023, and 029). The following table displays the number (percent) of all patients who received at least 1 dose of study therapy with clinical adverse experiences during the parenteral therapy period, during the parenteral therapy period plus 14 day safety follow-up period, and during the entire study period (study therapy period and follow-up period not limited to 14-days).

Clinical Adverse Experience Summary by Treatment Group

Number (%) of patients	Ertapenem 1 g (N=1954)†‡		Ertapenem 1.5 g (N=64)		Ertapenem 2 g (N=30)		P/T (N=774)†		CTX (N=942)†§		P/T + CTX (N=1716)	
	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Parenteral Therapy Period												
With one or more adverse experiences	928	(47.5)	46	(71.9)	11	(36.7)	434	(56.1)	444	(47.1)	878	(51.2)
With no adverse experience	1026	(52.5)	18	(28.1)	19	(63.3)	340	(43.9)	498	(52.9)	838	(48.8)
With drug-related adverse experiences%	390	(20.0)	8	(12.5)	3	(10.0)	171	(22.1)	187	(19.9)	358	(20.9)
With serious adverse experience	116	(5.9)	4	(6.3)	1	(3.3)	53	(6.8)	44	(4.7)	97	(5.6)
With serious drug-related adverse experience	15	(0.8)	0	(0.0)	0	(0.0)	2	(0.3)	2	(0.2)	4	(0.2)
Who died	12	(0.6)	2	(3.1)	0	(0.0)	3	(0.4)	0	(0.0)	3	(0.2)
Discontinued due to an adverse experience	83	(4.2)	3	(4.7)	1	(3.3)	40	(5.2)	36	(3.8)	76	(4.4)
Discontinued due to a drug-related adverse experience	24	(1.2)	0	(0.0)	0	(0.0)	12	(1.5)	6	(0.6)	18	(1.0)
Discontinued due to a serious adverse experience	51	(2.6)	1	(1.6)	1	(3.3)	17	(2.2)	22	(2.3)	39	(2.3)
Discontinued due to a serious drug-related adverse experience	10	(0.5)	0	(0.0)	0	(0.0)	1	(0.1)	2	(0.2)	3	(0.2)
Parenteral Period and 14-Day Follow-Up Period												
with one or more adverse experiences	1128	(57.7)	49	(76.6)	13	(43.3)	478	(61.8)	572	(60.7)	1050	(61.2)
with no adverse experience	826	(42.3)	15	(23.4)	17	(56.7)	296	(38.2)	370	(39.3)	666	(38.8)
with drug-related adverse experiences%	444	(22.7)	12	(18.8)	3	(10.0)	180	(23.2)	253	(26.9)	433	(25.2)
with serious adverse experiences	208	(10.7)	8	(12.5)	2	(6.7)	89	(11.5)	100	(10.6)	189	(11.0)
with serious drug-related adverse experiences	21	(1.1)	0	(0.0)	0	(0.0)	2	(0.3)	5	(0.5)	7	(0.4)
who died	35	(1.8)	3	(4.7)	0	(0.0)	12	(1.5)	15	(1.6)	27	(1.6)
discontinued due to an adverse experience	103	(5.2)	4	(6.3)	2	(6.7)	42	(5.4)	57	(6.1)	99	(5.8)
discontinued due to a drug-related adverse experience	33	(1.7)	1	(1.6)	0	(0.0)	13	(1.7)	13	(1.4)	26	(1.5)
discontinued due to a serious adverse experience	60	(3.0)	1	(1.6)	2	(6.7)	18	(2.3)	34	(3.6)	52	(3.0)
discontinued due to a serious drug-related adverse experience	12	(0.6)	0	(0.0)	0	(0.0)	1	(0.1)	2	(0.2)	3	(0.2)

† Includes patients with renal dose adjustments.
‡ Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
§ Includes patients who also received metronidazole.
% Determined by the investigator to be possibly, probably, or definitely drug related.
P/T = piperacillin/tazobactam.
CTX = ceftriaxone.

Clinical Adverse Experience Summary by Treatment Group (continued)

Number (%) of patients	Ertapenem 1 g (N=1954)[†‡]		Ertapenem 1.5 g (N=64)		Ertapenem 2 g (N=30)		P/T (N=775)[†]		CTX (N=942)[†§]		P/T + CTX (N=1716)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Entire Study Period												
With one or more adverse experiences	1128	(57.7)	49	(76.6)	13	(43.3)	478	(61.8)	572	(60.7)	1050	(61.2)
With no adverse experience	826	(42.3)	15	(23.4)	17	(56.7)	296	(38.2)	370	(39.3)	666	(38.8)
With drug-related adverse experiences[%]	444	(22.7)	12	(18.8)	3	(10.0)	180	(23.2)	253	(26.9)	433	(25.2)
With serious adverse experience	226	(11.6)	9	(14.1)	2	(6.7)	95	(12.6)	116	(12.3)	211	(12.3)
With serious drug-related adverse experience	22	(1.1)	0	(0.0)	0	(0.0)	2	(2.6)	6	(0.6)	8	(0.5)
Who died	47	(2.4)	4	(6.3)	0	(0.0)	15	(1.9)	21	(2.2)	36	(2.1)
Discontinued due to an adverse experience	103	(5.2)	4	(6.3)	2	(6.7)	42	(5.4)	57	(6.1)	99	(5.8)
Discontinued due to a drug-related adverse experience	33	(1.7)	1	(1.6)	0	(0.0)	13	(1.7)	13	(1.4)	26	(1.5)
Discontinued due to a serious adverse experience	60	(3.0)	1	(1.6)	2	(6.7)	18	(2.3)	34	(3.6)	52	(3.0)
Discontinued due to a serious drug-related adverse experience	12	(0.6)	0	(0.0)	0	(0.0)	1	(0.1)	2	(0.2)	3	(0.2)

[†] Includes patients with renal dose adjustments.
[‡] Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
[§] Includes patients who also received metronidazole.
[%] Determined by the investigator to be possibly, probably, or definitely drug related.
P/T = piperacillin/tazobactam.
CTX = ceftriaxone.

(Source: Compiled from Applicant's Tables E-21, E-50, E-51, E-53, E-56, and E-57 in the original NDA submission and Tables 25 and 36, July 3, 2001 submission to the NDA)

Medical Officer's Comment: ***The per protocol exposure to oral antimicrobial follow-up therapy in a large proportion of patients in the Applicant's safety database presents a possible confounding factor in the interpretation of the safety of ertapenem. The Applicant stated that for this reason, they have chosen to focus their safety discussion on the period of parenteral therapy only. During a pre-NDA telecon (January 28, 2000) between the Applicant and the Division, the Applicant was informed that the Division would look at both the parenteral therapy period and the entire study period in evaluating the risk versus benefit of ertapenem and that the Division would consider the data from the entire study period as the primary safety parameter.***

The protocols required collection of safety data through 14 days post completion of antimicrobial therapy, however, some investigators reported additional adverse events that occurred in the period between the 14 day follow-up safety period and the last follow-up study visit. Therefore the MO included a section in the previous table, designated "entire study period", to display all clinical adverse events occurring throughout the entire study period that were described by investigators. Inclusion of these additional data results in the reporting of slightly higher rates of serious adverse events, including deaths.

Overall, in each period, the incidence of clinical adverse events and serious clinical adverse events, both drug-related and non-drug-related were similar between the ertapenem 1 gm group (combined across all clinical studies) and the combined comparator group (P/T + CTX). The rates of discontinuation due to drug-related and non-drug-related adverse events were also similar across these groups.

Of the 3764 patients treated, 1127 (59.7%) in the ertapenem 1 gm group, 49 (76.6%) in the ertapenem 1.5 gm group, 13 (43.3%) in the ertapenem 2 gm group, 479 (61.8%) in the piperacillin/tazobactam group, and 572 (60.7%) in the ceftriaxone group had a clinical adverse experience during the during parenteral therapy period and the 14-day safety follow-up period. Compared to the parenteral therapy only period, these rates were higher for the larger treatment groups (an increase of 12.2% for ertapenem 1 gm, 5.7% for piperacillin/tazobactam, and 13.6% for ceftriaxone), as would be expected.

During the parenteral period plus 14-day follow-up period, clinical adverse experiences were observed most frequently in the gastrointestinal system. The most common of these were diarrhea (incidence for ertapenem 1 gm, 9.7% versus 6.8% during parenteral period, for ertapenem 1.5 gm 12.5% versus 9.4% during parenteral period, ertapenem 2 gm 6.7% versus 3.3% during parenteral period, piperacillin/tazobactam 12.1% versus 10.7% during parenteral period, and ceftriaxone 9.8% versus 5.9% during parenteral period), nausea (incidence for ertapenem 1 gm 7.3% versus 5.6% during parenteral period, for ertapenem 1.5 gm 15.6% versus 12.5% during parenteral period, ertapenem 2 gm 0% versus 0% during parenteral period, piperacillin/tazobactam 8.7% versus 7.2% during parenteral period, and ceftriaxone 7.4% versus 5.9% during parenteral period), and vomiting (incidence for ertapenem 1 gm 3.9% versus 3.0% during parenteral period, for ertapenem 1.5 gm 4.7% versus 3.1% during parenteral period, ertapenem 2 gm 0% versus 0% during parenteral period, piperacillin/tazobactam 5.3% versus 4.3% during parenteral period, and ceftriaxone 4.0% versus 3.1% during parenteral period).

Also relatively frequent were headache (incidence for ertapenem 1 gm, 6.3% versus 5.0%; for ertapenem 1.5 gm, 4.7% versus 4.7%; ertapenem 2 gm, 20.0%

versus 16.7%; piperacillin/tazobactam, 5.4% versus 4.7%; and ceftriaxone, 6.9% versus 6.2%, respectively during the parenteral plus 14-day follow-up period versus the parenteral period) and infused vein complications (incidence for ertapenem 1 gm, 6.1% versus 5.8%, for ertapenem 1.5 gm 3.1% versus 3.1%, ertapenem 2 gm 10.0% versus 10.0%; piperacillin/tazobactam 7.9% versus 7.8%, and ceftriaxone 6.7% versus 6.2%, respectively during the parenteral plus 14-day follow-up period versus the parenteral period).

The Applicant also examined all clinical adverse experience terms related to renal insufficiency for the parenteral therapy period and the 14-day safety follow-up period. The incidences of any terms for renal insufficiency (renal dysfunction, renal insufficiency, and acute renal insufficiency) were, for ertapenem 1 gm, 15/1954 (0.8%); ertapenem 1.5 gm 1/64 (1.6%); ertapenem 2 gm 0%; piperacillin/tazobactam 6/775 (0.8%); and ceftriaxone 8/942 (0.8%). While the rates of renal insufficiency increased in all major treatment groups after parenteral therapy, these increases were similar in the major treatment groups (the rate increased by 0.4% for ertapenem 1 gm, by 0.2% for piperacillin/tazobactam, and by 0.4% for ceftriaxone). Renal insufficiency was rarely considered drug related in the parenteral therapy period and the 14-day safety follow-up period; incidences were for ertapenem 1 gm 2/1954 (0.1%); ertapenem 1.5 gm and 2 gm (0%); piperacillin/tazobactam (0%); and ceftriaxone 1/942 (0.1%).

The following table displays the number (percent) of patients with specific clinical adverse experiences with an incidence ≥1% in one or more treatment groups by body system and drug relationship that occurred during parenteral therapy period and the 14-day safety follow-up period.

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥1 % in One or More Treatment Groups) by Body System During All Study Therapy and Follow-Up Period—All Clinical Studies (Total and Drug Related)

	Ertapenem 1 g (N=1954)[1]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[1]			Ceftriaxone (N=942)[1]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Patients with one or more adverse experiences	1127	(57.7)	454	49	(76.6)	12	13	(43.3)	3	478	(61.8)	180	572	(60.7)	253
Patients with no adverse experience	827	(42.3)		15	(23.4)		17	(56.7)		296	(38.2)		370	(39.3)	
Body as a Whole/Site Unspecified	**347**	**(17.8)**	**55**	**17**	**(26.6)**	**0**	**3**	**(10.0)**	**0**	**157**	**(20.3)**	**22**	**177**	**(18.8)**	**36**
Asthenia/fatigue	24	(1.2)	3	0	(0.0)	0	0	(0.0)	0	7	(0.9)	1	10	(1.1)	1
Death	35	(1.8)	0	3	(4.7)	0	0	(0.0)	0	12	(1.6)	0	15	(1.6)	0
Discharge, abdominal	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Distention, abdominal	15	(0.8)	0	3	(4.7)	0	0	(0.0)	0	13	(1.7)	1	9	(1.0)	2
Edema/swelling	60	(3.1)	3	3	(4.7)	0	0	(0.0)	0	19	(2.5)	2	31	(3.3)	2
Fever	66	(3.4)	3	7	(10.9)	0	0	(0.0)	0	51	(6.6)	1	32	(3.4)	2
Fungemia	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Hypothermia	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Infection	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Infection, bacterial	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Infection, fungal	10	(0.5)	5	0	(0.0)	0	0	(0.0)	0	5	(0.6)	5	10	(1.1)	7
Multiple organ failure	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Pain	11	(0.6)	3	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	12	(1.3)	4
Pain, abdominal	78	(4.0)	17	4	(6.3)	0	1	(3.3)	0	27	(4.8)	4	39	(3.9)	12
Pain, chest	24	(1.2)	3	0	(0.0)	0	1	(3.3)	0	11	(1.4)	0	24	(2.5)	1
Pain, postoperative	13	(0.7)	0	1	(1.6)	0	0	(0.0)	0	15	(1.9)	0	4	(0.4)	0
Postoperative complication	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Septicemia	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	2	(0.2)	0
Shock, septic	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	1	(0.1)	0
Surgery, abdominal	1	(0.1)	0	2	(3.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Trauma	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	1	0	(0.0)	0
Warmth, injection site	0	(0.0)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Cardiovascular System	**304**	**(15.6)**	**114**	**14**	**(21.9)**	**3**	**4**	**(13.3)**	**1**	**165**	**(21.3)**	**60**	**162**	**(17.2)**	**67**
Arrhythmia	6	(0.3)	1	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	0
Asystole	3	(0.2)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Atherosclerosis, coronary	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Atrial fibrillation	5	(0.3)	0	3	(4.7)	0	0	(0.0)	0	6	(0.8)	0	4	(0.4)	1
Blood pressure increased	8	(0.4)	1	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	6	(0.6)	0
Bradycardia	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Extravasation	23	(1.2)	8	0	(0.0)	0	0	(0.0)	0	13	(1.7)	6	10	(1.1)	4
Heart failure	12	(0.6)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	8	(0.8)	0
Hematoma	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	0	(0.0)	0
Hemorrhage	2	(0.1)	1	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	0	(0.0)	0
Hypertension	21	(1.1)	0	2	(3.1)	0	0	(0.0)	0	11	(1.4)	1	9	(1.0)	1
Hypotension	28	(1.4)	3	3	(4.7)	0	0	(0.0)	0	11	(1.4)	1	11	(1.2)	1
Idioventricular rhythm	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, infused vein	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Infused vein complication	119	(6.1)	73	2	(3.1)	2	3	(10.0)	1	61	(7.9)	43	63	(6.7)	43
Left bundle branch block	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Murmur, heart	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Peripheral pulse decreased	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Peripheral vascular disorder	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Phlebitis/thrombophlebitis	33	(1.7)	25	1	(1.6)	1	0	(0.0)	0	21	(2.7)	10	19	(2.0)	14
Supraventricular tachycardia	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0
T-wave abnormality	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Tachycardia	28	(1.4)	1	1	(1.6)	0	1	(3.3)	0	10	(1.3)	0	7	(0.7)	0
Thrombosis, deep vein	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	1	3	(0.3)	0
Ventricular tachycardia	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0

	Ertapenem 1 g (N=1954)[1]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[1]			Ceftriaxone (N=942)[1]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Digestive System	**500**	**(25.6)**	**214**	**32**	**(50.0)**	**7**	**2**	**(6.7)**	**1**	**244**	**(31.5)**	**89**	**250**	**(26.5)**	**115**
Acid regurgitation	26	(1.3)	6	0	(0.0)	0	0	(0.0)	0	7	(0.9)	2	6	(0.6)	0
Anorexia	9	(0.5)	3	1	(1.6)	0	0	(0.0)	0	9	(1.2)	0	7	(0.7)	1
Appetite change	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ascites	2	(0.1)	0	2	(3.1)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Candidiasis, oral	17	(0.9)	9	1	(1.6)	0	0	(0.0)	0	10	(1.3)	9	18	(1.9)	13
Cholelithiasis	3	(0.2)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	1	(0.1)	0
Constipation	70	(3.6)	7	6	(9.4)	0	0	(0.0)	0	42	(5.4)	6	29	(3.1)	2
Diarrhea	189	(9.7)	107	8	(12.5)	3	2	(6.7)	1	94	(12.1)	54	92	(9.8)	56
Discoloration, tongue	0	(0.0)	0	1	(1.6)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dry mouth	11	(0.6)	6	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	11	(1.2)	8
Dyspepsia	21	(1.1)	7	1	(1.6)	0	1	(3.3)	0	5	(0.6)	2	15	(1.6)	1
Eating habits	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Enterocolitis, pseudomembranous	2	(0.1)	2	1	(1.6)	1	0	(0.0)	0	0	(0.0)	0	3	(0.3)	2
Hematochezia	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0
Hemorrhage, anal/rectal	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Ileus	6	(0.3)	0	2	(3.1)	0	0	(0.0)	0	13	(1.7)	0	2	(0.2)	0
Incontinence, fecal	2	(0.1)	1	1	(1.6)	0	0	(0.0)	0	4	(0.5)	1	1	(0.1)	0
Infection, intra-abdominal	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	16	(2.1)	1	8	(0.8)	1
Intubation, gastric, complication	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Nausea	142	(7.3)	61	10	(15.6)	2	0	(0.0)	0	67	(8.7)	26	70	(7.4)	31
Obstruction, intestinal	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	1	(0.1)	0
Pancreas disorder	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Surgery, intestinal, complication	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Ulcer, duodenal w/perforation	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Vomiting	76	(3.9)	22	3	(4.7)	0	0	(0.0)	0	41	(5.3)	13	38	(4.0)	11
Endocrine System	**9**	**(0.5)**	**0**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**3**	**(0.4)**	**0**	**4**	**(0.4)**	**0**
Diabetes, loss of control	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypothyroidism	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Hemic and Lymphatic System	**39**	**(2.0)**	**3**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**11**	**(1.4)**	**0**	**14**	**(1.5)**	**0**
Anemia	21	(1.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	6	(0.6)	0
Petechiae	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Metabolic, Nutritional, Immune	**55**	**(2.8)**	**4**	**9**	**(14.1)**	**0**	**0**	**(0.0)**	**0**	**17**	**(2.2)**	**1**	**38**	**(4.0)**	**3**
Acidosis	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	4	(0.4)	0
BUN increased	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dehydration	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	9	(1.0)	1
Electrolyte imbalance	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Fluid overload	1	(0.1)	0	4	(6.3)	0	0	(0.0)	0	1	(0.1)	0	4	(0.4)	0
Hyperglycemia	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	5	(0.5)	0
Hypoglycemia	5	(0.3)	1	2	(3.1)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	0
Hypokalemia	6	(0.3)	0	2	(3.1)	0	0	(0.0)	0	3	(0.4)	0	6	(0.6)	0
Musculoskeletal System	**90**	**(4.6)**	**5**	**2**	**(3.1)**	**0**	**1**	**(3.3)**	**0**	**38**	**(4.9)**	**3**	**48**	**(5.1)**	**4**
Arthritis	1	(0.1)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Pain, back	13	(0.7)	0	2	(3.1)	0	0	(0.0)	0	11	(1.4)	1	18	(1.9)	0
Nervous System and Psychiatric Disorder	**323**	**(16.5)**	**79**	**17**	**(26.6)**	**2**	**6**	**(20.0)**	**3**	**140**	**(18.1)**	**23**	**157**	**(16.7)**	**40**
Agitation	18	(0.9)	2	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	3	(0.3)	0
Anxiety	20	(1.0)	1	0	(0.0)	0	0	(0.0)	0	10	(1.3)	1	11	(1.2)	0
Confusion	39	(2.0)	4	5	(7.8)	1	0	(0.0)	0	14	(1.8)	2	8	(0.8)	0
Depression	6	(0.3)	1	1	(1.6)	0	0	(0.0)	0	8	(1.0)	1	2	(0.2)	0
Dizziness	34	(1.7)	14	1	(1.6)	0	0	(0.0)	0	23	(3.0)	5	20	(2.1)	7
Hallucinations	6	(0.3)	1	2	(3.1)	1	0	(0.0)	0	3	(0.4)	1	3	(0.3)	1
Headache	123	(6.3)	43	3	(4.7)	0	6	(20.0)	3	42	(5.4)	9	65	(6.9)	22

	Ertapenem 1 g (N=1954)[*]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[†]			Ceftriaxone (N=942)[‡§]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Insomnia	61	(3.1)	6	3	(4.7)	0	0	(0.0)	0	40	(5.2)	1	39	(4.1)	1
Mental status change	6	(0.3)	0	1	(1.6)	1	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Nervousness	9	(0.5)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0
Somnolence	22	(1.1)	8	1	(1.6)	0	1	(3.3)	0	6	(0.8)	1	10	(1.1)	7
Respiratory System	**279**	**(14.3)**	**12**	**17**	**(26.6)**	**1**	**5**	**(16.7)**	**0**	**107**	**(13.8)**	**2**	**138**	**(14.6)**	**7**
Atelectasis	9	(0.5)	0	2	(3.1)	0	0	(0.0)	0	8	(1.0)	0	2	(0.2)	0
Chest sound abnormality	9	(0.5)	0	3	(4.7)	0	0	(0.0)	0	9	(1.2)	0	3	(0.3)	1
Congestion, pulmonary	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Cough	28	(1.4)	1	1	(1.6)	0	0	(0.0)	0	13	(1.7)	0	5	(0.5)	0
Cough decreased	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dyspnea	33	(1.7)	3	4	(6.3)	1	1	(3.3)	0	14	(1.8)	0	23	(2.4)	2
Edema, pulmonary	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	0
Effusion, pleural	25	(1.3)	0	4	(6.3)	0	0	(0.0)	0	12	(1.6)	0	18	(1.9)	0
Epistaxis	8	(0.4)	1	1	(1.6)	0	0	(0.0)	0	5	(0.6)	2	3	(0.3)	0
Hiccups	3	(0.2)	0	2	(3.1)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Hypoxemia	20	(1.0)	0	1	(1.6)	0	0	(0.0)	0	7	(0.9)	0	4	(0.4)	0
Infection, respiratory	3	(0.2)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Infection, respiratory, upper	12	(0.6)	0	1	(1.6)	0	0	(0.0)	0	7	(0.9)	0	7	(0.7)	0
Infiltrate, pulmonary	3	(0.2)	0	1	(1.6)	0	1	(3.3)	0	1	(0.1)	0	1	(0.1)	0
Mediastinum disorder	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pain, pleuritic	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	4	(0.4)	0
Pharyngitis	19	(1.0)	0	2	(3.1)	0	0	(0.0)	0	11	(1.4)	0	6	(0.6)	0
Pneumonia	28	(1.4)	1	2	(3.1)	0	2	(6.7)	0	9	(1.2)	0	15	(1.6)	0
Rales/rhonchi	15	(0.8)	1	2	(3.1)	0	0	(0.0)	0	8	(1.0)	0	9	(1.0)	0
Respiratory distress	10	(0.5)	0	4	(6.3)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0
Respiratory insufficiency	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Tachypnea	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0
Wheezing	15	(0.8)	1	1	(1.6)	0	1	(3.3)	0	8	(1.0)	0	9	(1.0)	0
Skin and Skin Appendage	**222**	**(11.4)**	**46**	**10**	**(15.6)**	**0**	**3**	**(10.0)**	**0**	**125**	**(16.1)**	**31**	**95**	**(10.1)**	**28**
Dehiscence, wound	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Delay, wound healing	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Erythema	27	(1.4)	4	1	(1.6)	0	0	(0.0)	0	13	(1.7)	3	11	(1.2)	5
Herpes simplex	14	(0.7)	1	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	11	(1.2)	4
Herpes zoster	6	(0.3)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Induration	0	(0.0)	0	1	(1.6)	0	1	(3.3)	0	1	(0.1)	0	3	(0.3)	3
Infection, wound	14	(0.7)	0	0	(0.0)	0	0	(0.0)	0	16	(2.1)	0	1	(0.1)	1
Infection, wound, postoperative	7	(0.4)	1	2	(3.1)	0	0	(0.0)	0	7	(0.9)	0	0	(0.0)	0
Pruritus	28	(1.4)	16	0	(0.0)	0	0	(0.0)	0	20	(2.6)	9	18	(1.9)	9
Rash	46	(2.4)	22	0	(0.0)	0	1	(3.3)	0	24	(3.1)	14	14	(1.5)	6
Sweating	11	(0.6)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	1	5	(0.5)	0
Ulcer, decubitus	4	(0.2)	0	2	(3.1)	0	0	(0.0)	0	1	(0.1)	0	5	(0.5)	0
Ulcer, skin	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	0	(0.0)	0
Special Senses	**33**	**(1.7)**	**7**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**10**	**(1.3)**	**3**	**22**	**(2.3)**	**8**
Intraocular pressure increase	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Irritation, eyelid	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Keratitis	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Urogenital System	**146**	**(7.5)**	**40**	**11**	**(17.2)**	**1**	**0**	**(0.0)**	**0**	**66**	**(8.5)**	**7**	**86**	**(9.1)**	**28**
Cyst, kidney	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Infection, urinary tract	16	(0.8)	2	2	(3.1)	0	0	(0.0)	0	10	(1.3)	1	11	(1.2)	0
Menstruation disorder	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Oliguria/anuria	8	(0.4)	0	3	(4.7)	0	0	(0.0)	0	9	(1.2)	0	2	(0.2)	0
Pain, testicle	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Renal insufficiency	12	(0.6)	1	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0
Urinary incontinence	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	6	(0.6)	0
Urination disorder	3	(0.2)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Urine abnormality	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Vaginitis	26	(1.3)	22	1	(1.6)	1	0	(0.0)	0	4	(0.5)	3	18	(1.9)	17

[*] Includes patients with renal dose adjustments.
[†] Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
[‡] Includes patients who also received metronidazole.
N = Number of treated patients in the treatment group. n = Number of patients reporting clinical adverse experiences. DR = Drug related.
Number of patients reporting clinical adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had an adverse experience.

(Table E-51, September 21, 2001 submission)

Medical Officer's Comment: ***The incidence of drug-related and non-drug-related clinical adverse experiences occurring in ≥1% of patients was similar, in most cases (see discussion of deaths in section 7.2.6), between the ertapenem 1 gm group and the combined comparator group (P/T + CTX) for both the parenteral therapy period alone and for the parenteral therapy plus 14-day safety follow-up period.***

The following table displays the number (percent) of patients with specific drug-related clinical adverse experiences with an incidence ≥1% in one or more treatment groups (ertapenem 1 gm, piperacillin/tazobactam, ceftrixone, and combined piperacillin/tazobactam + ceftriaxone) by body system and drug relationship that occurred during parenteral therapy period and the 14-day safety follow-up period.

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Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence >1% in One or More Treatment Groups) by Body System During All Study Therapy and Follow-Up Period–All Clinical Studies (Drug Related)

	Ertapenem 1 g (N=1954)[†‡]		P/T (N=774)[†]		CTX (N=942)[‡§]		P/T +CTX (N=1716)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences[%]	454	(23.2)	180	(23.3)	253	(26.9)	433	(25.2)
Patients with no drug-related adverse experience	1500	(76.8)	594	(76.7)	689	(73.1)	1283	(74.8)
Body as a Whole/Site Unspecified	**55**	**(2.8)**	**22**	**(2.8)**	**36**	**(3.8)**	**58**	**(3.4)**
Pain, abdominal	17	(0.9)	4	(0.5)	12	(1.3)	16	(0.9)
Cardiovascular System	**114**	**(5.8)**	**60**	**(7.8)**	**67**	**(7.1)**	**127**	**(7.4)**
Infused vein complication	73	(3.7)	43	(5.6)	43	(4.6)	86	(5.0)
Phlebitis/thrombophlebitis	25	(1.3)	10	(1.3)	14	(1.5)	24	(1.4)
Digestive System	**214**	**(11.0)**	**89**	**(11.5)**	**115**	**(12.2)**	**204**	**(11.9)**
Candidiasis, oral	9	(0.5)	9	(1.2)	13	(1.4)	22	(1.3)
Diarrhea	107	(5.5)	54	(7.0)	56	(5.9)	110	(6.4)
Nausea	61	(3.1)	26	(3.4)	31	(3.3)	57	(3.3)
Vomiting	22	(1.1)	13	(1.7)	11	(1.2)	24	(1.4)
Hemic and Lymphatic System	**3**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Metabolic, Nutritional, Immune	**4**	**(0.2)**	**1**	**(0.1)**	**3**	**(0.3)**	**4**	**(0.2)**
Musculoskeletal System	**5**	**(0.3)**	**3**	**(0.4)**	**4**	**(0.4)**	**7**	**(0.4)**
Nervous System and Psychiatric Disorder	**79**	**(4.0)**	**23**	**(3.0)**	**40**	**(4.2)**	**63**	**(3.7)**
Headache	43	(2.2)	9	(1.2)	22	(2.3)	31	(1.8)
Respiratory System	**12**	**(0.6)**	**2**	**(0.3)**	**7**	**(0.7)**	**9**	**(0.5)**
Skin and Skin Appendage	**46**	**(2.4)**	**31**	**(4.0)**	**28**	**(3.0)**	**59**	**(3.4)**
Pruritus	16	(0.8)	9	(1.2)	9	(1.0)	18	(1.0)
Rash	22	(1.1)	14	(1.8)	6	(0.6)	20	(1.2)
Special Senses	**7**	**(0.4)**	**3**	**(0.4)**	**8**	**(0.8)**	**11**	**(0.6)**
Urogenital System	**40**	**(2.0)**	**7**	**(0.9)**	**28**	**(3.0)**	**35**	**(2.0)**
Vaginitis	22	(1.1)	3	(0.4)	17	(1.8)	20	(1.2)

[†]Includes patients with renal dose adjustments.
[‡]Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
[§]Includes patients who also received metronidazole.
[%]Determined by the investigator to be possibly, probably, or definitely drug related.
P/T = Piperacillin/tazobactam.
CTX = Ceftriaxone.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least one patient had a drug-related adverse experience.
(Table E-52 [modified to include combined comparator data], September 21, 2001 submission)

Medical Officer's Comment: ***The incidence of drug-related clinical adverse experiences was similar between the ertapenem 1 gm group and the combined comparator group (P/T + CTX) for both the parenteral therapy period alone and for the parenteral therapy plus 14-day safety follow-up period.***

Of note, when the Applicant calculated the incidence of drug-related vaginitis they used the overall population (male and female) as the denominator. The MO believes it would be more appropriate to use only the female population in determining the incidence rates for this adverse event. With this adjustment the incidence of drug-related vaginitis in female patients was 22/1045 (2.1%) for ertapenem 1 gm, 3/406 (0.7%) for piperacillin/tazobactam, 17/481 (3.5%) for ceftriaxone, and 20/887 (2.3%) for the combined comparator group.

Based on the data in the preceding table the Medical Officer recommends that the following drug-related adverse events occurring in ≥1% of patients receiving ertapenem 1 gm daily be specifically noted in the "Adverse Reactions" section of the label: infused vein complication (3.7%), phlebitis/thrombophlebitis (1.3%), diarrhea (5.5%), nausea (3.1%), vomiting (1.1%), headache (2.2%), rash (1.1%), and vaginitis (2.1%).

7.2.6 Deaths

Phase I Studies

No deaths occurred in the Phase I studies.

Phase II and III Studies

Overall, there were 86 deaths (2.4%) reported during the entire study period (study therapy and follow-up not limited to 14 days): 47 deaths (2.4%) in the ertapenem 1 gm group, 4 deaths (6.3%) in the ertapenem 1.5 gm group, 0 deaths in the ertapenem 2 gm group, 15 deaths (1.9%) in the piperacillin/tazobactam group, and 21 deaths (2.2%) in the ceftriaxone group. None of the deaths was considered study drug related. Narratives for patients that died during the entire study period are in Appendix 28.

According to the Applicant the majority of deaths and fatal serious adverse experiences had onset or occurred while patients were off parenteral study drug. The following table displays the number (%) of patients that died during the parenteral therapy period and during the entire study period.

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Number (%) of Patients With Serious Clinical Adverse Experience of Death During Entire Study—All Clinical Studies (Total and Drug Related)

	Ertapenem 1 g (N=1953)[1,2]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			P/T (N=775)[3]			CTX (N=942)[3,5]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Parenteral Therapy Period	11	(0.8)	0	2	(3.1)	0	0	(0.0)	0	3	(0.4)	0	0	(0.0)	0
Entire Study	47	(2.4)	0	4	(6.3)	0	0	(0.0)	0	15	(1.9)	0	21	(2.2)	0

[1] Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
[2] Includes patients with renal dose adjustments.
[3] Includes patients who also received metronidazole.
Entire study includes study therapy and entire follow-up period, not limited to 14 days.
P/T = piperacillin/tazobactam.
CTX = ceftriaxone.
N = Number of treated patients in the treatment group.
n = Number of patients reporting clinical adverse experiences.
DR = Drug related. Number of patients reporting clinical adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.

(From Applicant's Table E-53, original NDA submission: Applicant's Table 25 and Table 27, July 3, 2001 submission: Applicant's Table 4, August 24, 2001 submission)

The Applicant, at the Medical Officer's request, provided additional analyses of the deaths that occurred in the clinical studies by treatment phase and group in their August 24, 2001 submission to the NDA. In this submission they included a breakdown of ertapenem 1 gm group deaths by the cohort (pipercillin/tazobactam or ceftriaxone) with which they were enrolled and provided statistical analyses comparing deaths between groups. The following table displays the data submitted.

Analysis of Incidence of Death -
All Clinical Studies
(Treated Patients)

Ertapenem 1 g (A)		Comparator (B)		Exact P-value (A versus B)	
Ceftriaxone cohort	Piperacillin/ Tazobactam Cohort	Ceftriaxone	Piperacillin/ Tazobactam	Relative Risk Test	Difference Test
During Parenteral Therapy					
2/1065 (0.2%)	9/801 (1.1%)	0/912 (0%)	3/775 (0.4%)	NA * 0.306	0.503 0.145
During Study Therapy plus 14 Day Follow-Up Period					
14/1065 (1.3%)	20/801 (2.5%)	15/912 (1.6%)	12/775 (1.5%)	0.680 0.335	0.577 0.213
During Entire Study Period					
20/1065 (1.9%)	26/801 (3.2%)	21/912 (2.3%)	15/775 (1.9%)	0.647 0.205	0.530 0.115

* Relative risk is not calculated when the denominator is zero.
NA = not applicable.

(Applicant's Table 5, August 24, 2001 submission)

Medical Officer's Comment: *Of note, this table does not include deaths from protocol 029=1 death in ertapenem 1 gm group on parenteral therapy. It is also notable that 1 death in the piperacillin/tazobactam group is actually derived from the ertapenem 1.5 g cohort of enrollees from study 017 and since only deaths from the 1 gm cohort are included in the Applicant's display of the ertapenem group, it would be more appropriate to exclude this patient.*

The Applicant also provided a summary table that displayed the number of deaths by treatment group for each clinical study.

Clinical Adverse Experience Summary by Treatment Group- All Clinical Studies

	Ertapenem 1 g (N=1953)[‡;]		Ertapenem 1.5 g (N=64)		Ertapenem 2 g (N=30)		P/T (N=775)[†]		CTX (N=942)[‡§]	
	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Mortality duirng Parenteral Therapy										
Protocol 002C	0/28	(0)	—	—	0/30	(0)	—	—	0/28	(0)
Protocol 004	0/57	(0)	1/50	(2.0)	—	—	—	—	0/109	(0)
Protocol 014	0/293	(0)	—	—	—	—	—	—	0/289	(0)
Protocol 016	0/271	(0)	—	—	—	—	1/258	(0.4)	—	—
Protocol 017	8/316	(2.5)	1/14	(7.1)	—	—	2/325	(0.6)	—	—
Protocol 018	2/242	(0.8)	—	—	—	—	—	—	0/256	(0)
Protocol 020	0/236	(0)	—	—	—	—	—	—	0/123	(0)
Protocol 021	0/175	(0)	—	—	—	—	—	—	0/83	(0)
Protocol 023	1/214	(0.5)	—	—	—	—	0/192	(0)	—	—
Protocol 029	1/87	(1.1)	—	—	—	—	—	—	0/30	(0)
Overall	**12/1953**	**(0.6)**	**2/64**	**(3.1)**	**0/30**	**(0.0)**	**3/775**	**(0.4)**	**0/942**	**(0.0)**
versus CRO	3/1152	(0.3)	1/50	(2.0)	0/30	(0.0)	—	—	0/912	(0.0)
versus P/T	9/801	(1.1)	1/14	(7.1)	—	—	3/775	(0.4)	—	—
Mortality during Study Therapy plus the 14-day Follow-Up Period										
Protocol 002C	0/28	(0)	—	—	0/30	(0)	—	—	2/27	(7.4)
Protocol 004	1/57	(1.8)	1/50	(2.0)	—	—	—	—	3/109	(2.8)
Protocol 014	3/293	(1.0)	—	—	—	—	—	—	1/289	(0.3)
Protocol 016	3/271	(1.1)	—	—	—	—	3/258	(1.2)	—	—
Protocol 017	15/316	(4.8)	2/14	(14.3)	—	—	9/325	(2.8)	—	—
Protocol 018	7/242	(2.9)	—	—	—	—	—	—	5/256	(2.0)
Protocol 020	2/236	(0.8)	—	—	—	—	—	—	3/123	(2.4)
Protocol 021	1/175	(0.6)	—	—	—	—	—	—	1/83	(1.2)
Protocol 023	2/214	(0.9)	—	—	—	—	0/192	(0)	—	—
Protocol 029	1/87	(1.1)	—	—	—	—	—	—	0/30	(0)
Overall	**35/1953**	**(1.8)**	**3/64**	**(4.7)**	**0/30**	**(0)**	**12/775**	**(1.5)**	**15/942**	**(1.6)**
versus CRO	15/1152	(1.3)	1/50	(2.0)	0/30	(0)	—	—	15/942	(1.6)
versus P/T	20/801	(2.5)	2/14	(14.3)	—	—	12/775	(1.5)	—	—
Mortality during the Entire Study Period (Study Therapy and Follow-Up not Limited to 14 Days)										
Protocol 002C	0/28	(0)	—	—	0/30	(0)	—	—	2/27	(7.4)
Protocol 004	1/57	(1.8)	2/50	(4.0)	—	—	—	—	6/109	(5.5)
Protocol 014	3/293	(1.0)	—	—	—	—	—	—	3/289	(1.0)
Protocol 016	4/271	(1.5)	—	—	—	—	3/258	(1.2)	—	—
Protocol 017	20/316	(6.3)	2/14	(14.3)	—	—	12/325*	(3.7)	—	—
Protocol 018	8/242	(3.3)	—	—	—	—	—	—	6/256	(2.3)
Protocol 020	5/236	(2.1)	—	—	—	—	—	—	3/123	(2.4)
Protocol 021	3/175	(1.7)	—	—	—	—	—	—	1/83	(1.2)
Protocol 023	2/214	(0.9)	—	—	—	—	0/192	(0)	—	—
Protocol 029	1/87	(1.1)	—	—	—	—	—	—	0/30	(0)
Overall	**47/1953**	**(2.4)**	**4/64**	**(6.3)**	**0/30**	**(0)**	**15/775***	**(1.9%)**	**21/942**	**(2.2%)**
versus CRO	21/1152	(1.8)	2/50	(4.0)	0/30	(0)	—	—	21/942	(2.2%)
versus P/T	26/801	(3.2)	2/14	(14.3)	—	—	15/775*	(1.9%)	—	—

* Includes AN 5052 who was enrolled in the 1.5 gm cohort of patients in study 017
† Includes patients with renal dose adjustments.
‡ Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
§ Includes patients who also received metronidazole.
% Determined by the investigator to be possibly, probably, or definitely drug related.
N = number of patients. n/m = number of patients that died/number of patients enrolled.
P/T=Piperacillin/tazobactam. CTX=Ceftriaxone.

(Applicant's Table 4, August 24, 2001 submission-modified to include death data from study 029)

Medical Officer's Comment: ***In determining the number of patients that died during the parenteral therapy period, the Applicant counted only those patients who died that were listed in data sets as on IV therapy. Therefore patients that may have been discontinued from study drug, but died while still having significant levels of study drug circulating may have not been counted by the Applicant as a death***

during parenteral therapy. In the MO's table below, if a patient died within 1 day of discontinuing parenteral therapy they were counted as a death in the parenteral therapy period (calculated from January 10, 2001 submission, AE.XPT, PREFTERM=DEATH and TIMONSET=≤1).

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Number (%) of Patients With Serious Clinical Adverse Experiences (Incidence ≥1% in One or More Treatment Groups) by Body System During Entire Study—All Clinical Studies According to the Medical Officer (Total and Drug Related)

	Ertapenem 1 g** (N=1953)[‡‡]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			P/T (N=775)[†]			CTX* (N=942)[‡§]			P/T + CTX (N=1717)		
Parenteral Therapy Period	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	%	DR
	18	(0.9)	0	3	(4.7)	0	0	(0.0)	0	6*	(0.8)	0	5	(0.5)	0	11	(0.6)	0
Entire Study Period																		
	47	(2.4)	0	4	(6.3)	0	0	(0.0)	0	15*	(1.9)	0	21	(2.2)	0	36	(2.1)	0

* Includes AN 5052 who was enrolled in the 1.5 gm cohort of patients in study 017
** Includes patients from study 029 submitted in July 3, 2001 submission.
† Includes patients randomized to 1 g but dose adjusted to 2 g (5 patients in the ertapenem 1-g group and 5 patients in the ceftriaxone group).
‡ Includes patients with renal dose adjustments.
§ Includes patients who also received metronidazole.
Entire study includes study therapy and entire follow-up period, not limited to 14 days.
P/T = piperacillin/tazobactam.
CTX = ceftriaxone.
N = Number of treated patients in the treatment group.
n = Number of patients reporting clinical adverse experiences.
DR = Drug related. Number of patients reporting clinical adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related.

Based on the MO's classification of patients in the parenteral therapy period and entire study period, the revised breakdown of ertapenem 1 gm group deaths by the cohort (pipercillin/tazobactam or ceftriaxone) with which they were enrolled, and statistical analyses (performed by Dr. George Rochester, FDA Biometrics reviewer) comparing deaths between groups are provided in the following table.

**Analysis of Incidence of Death -
All Clinical Studies
According to the Medical Officer
(Treated Patients)**

Ertapenem 1 g (A)		Comparator (B)		Exact P-value (A versus B)	
Ceftriaxone cohort	Piperacillin/ Tazobactam Cohort	Ceftriaxone	Piperacillin/ Tazobactam	Relative Risk~ Test	Difference` Test
During Parenteral Therapy					
6/1152 (0.5%)	12/801 (1.5%)	5/942 (0.5%)	6/775* (0.8%)	1.000 0.348	1.000 0.236
During Entire Study Period					
21/1152 (1.8%)	26/801 (3.2%)	21/942 (2.2%)	15/775 *(1.9%)	0.734 0.205	0.534 0.115

*Includes AN 5052 who was enrolled in the 1.5 gm cohort of patients in study 017
~Exact p-value for relative risk comparison (Proc StatXact)
` Fisher's exact test.
(Note: Death data from Protocol 029 is included in this table)

The trend for more deaths in the ertapenem 1 gm pipercillin/tazobactam cohort resulted primarily from deaths that occurred in the pivotal intra-abdominal infections study (P017). At the MO's request, the Applicant provided a more detailed review of this group of patients in their August 24, 2001 submission. Based on the Applicant's additional analyses, they believe that the greater incidence of death in the ertapenem 1 gm group in this study resulted from a greater proportion of patients in the ertapenem 1 gm group that had an APACHE II score ≥20 and thus a greater predicted mortality. The Applicant's table displaying more detailed mortality and baseline APACHE II scores from Protocol 017 follows:

Baseline Disease Characteristics - Protocol 017 Treated Patients

	Ertapenem 1 g (N=316)	Ertapenem 1.5 g (N=14)	Piperacillin/ Tazobactam (N=325)	Total (N=655)
	N (%)	n (%)	n (%)	n (%)
Mortality				
During Parenteral Therapy	8 (2.5)	1 (7.1)	2 (0.6)	11 (1.7)
During Study Therapy plus the 14-day Follow-Up Period	15 (4.8)	2 (14.3)	9 (2.8)	26 (4.0)
During the Entire Study Period (Study Therapy And Follow-Up not Limited to 14 Days)	20 (6.3)	2 (14.3)	12 (3.7)	34 (5.2)
Stratum†				
Complicated Appendicitis APACHE II ≤15	116 (36.7)	4 (28.6)	118 (36.3)	238 (36.4)
Complicated Appendicitis APACHE II >15	2 (0.6)	0 (0)	4 (1.2)	6 (0.9)
Other Diagnoses APACHE II ≤ 15	176 (55.7)	6 (42.9)	185 (56.9)	367 (56.0)
Other Diagnoses APACHE II >15	22 (7.0)	4 (28.6)	17 (5.2)	43 (6.6)
Unknown	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Apache Score				
Unknown	0 (0)	0 (0)	1 (0.3)	1 (0.2)
0-4	93 (29.4)	1 (7.1)	92 (28.3)	186 (28.4)
5-9	130 (41.1)	4 (28.6)	139 (42.8)	273 (41.7)
10-14	60 (19.0)	5 (35.7)	64 (19.7)	129 (19.7)
15-19	20 (6.3)	2 (14.3)	23 (7.1)	45 (6.9)
20-24	9 (2.9)	2 (14.3)	5 (1.5)	16 (2.4)
>25	4 (1.3)	0 (0)	1 (0.3)	5 (0.8)
Unknown	0 (0)	0 (0)	1 (0.3)	1 (0.2)
APACHE II Score ≤ 15	292 (92.4)	10 (71.4)	303 (93.2)	605 (92.4)
APACHE II Score >15	24 (7.6)	4 (28.6)	21 (6.5)	49 (7.5)

† Stratification errors are corrected in this table (see Section II.6.2 of the Protocol 017 Clinical Study Report).
N = number of treated patients in treatment group.
n/m = number of patients with category of failure/number of patients that failed.
SD = Standard deviation.

(Applicant's Table 6, August 24, 2001 submission)

When the Applicant further displayed the observed deaths in study 017 by subsets of APACHE score a trend for higher mortality in the ertapenem 1 gm group remained in all but the APACHE >25 group. As was noted previously, 1 death in the piperacillin/tazobactam group AN 5052, APACHE score =14 is actually derived from the ertapenem 1.5 g cohort of enrollees from study 017. The following table displays the mortality during the entire study period by baseline APACHE score.