Mortality by Baseline APACHE II Score During Entire Study
Protocol 017

APACHE Score	Expected Mortality[1]		Observed Mortality					
	Assumption 1[2] (%)	Assumption 2[3] (%)	Ertapenem 1 g		Piperacillin/ Tazobactam		Total	
			n/m	(%)	n/m	(%)	n/m	(%)
0 - 4	0 - 5	0 - 8	0/93	(0)	0/92	(0)	0/185	(0)
5 - 9	6 - 10	9 - 15	7/130	(5.4)	5/139	(3.6)	12/269	(4.5)
10 - 14	12 - 20	17 - 27	4/60	(6.7)	2/64	(3.1)	6/124	(4.8)
15 - 19	22 - 33	30 - 44	5/20	(25.0)	4/23	(17.4)	9/43	(21.0)
20 - 24	37 - 51	48- 62	3/9	(33.3)	0/5	(0)	3/14	(21.4)
25 - 30	55 - 72	65 - 89	1/4	(25.0)	1/1	(100)	2/5	(40.0)
Overall			20/316	(6.3)	12/324	(3.7)	32/640	(5.0)

n/m = Number of deaths/ number of patients in the APACHE score category in the treatment group.
[1]Calculated as described in (NDA 21-337, Item 8, Ref. 147).
[2]Assuming standard (not post-emergency) postoperative ICU admission for GI perforation/obstruction without sepsis.
[3]Assuming sepsis (non-operative weighting) from GI source and non-post-emergency surgery.

(Applicant's Table 9, August 24, 2001 submission)

Medical Officer's Comment: ***While the death rate was lower than predicted for both groups overall, the persistent trend for higher death rates in the ertapenem 1 gm group compared to the piperacillin/tazobactam group in this study is concerning. The MO has further reviewed the case report forms and Applicant's data sets for patients in study 017 and does not believe there were any clinically significant differences in concurrent therapies, medical histories, or baseline microbiology between the treatment groups.***

Given a trend for an increased incidence of death for the ertapenem group in study 017, the Medical Officer recommends that the discrepancy in death rates in P017 be specifically noted in the "Adverse Reactions" section of the label.[11] The Medical Officer also recommends that the Applicant be required to provide additional data regarding incidence of death in patients with complicated intra-abdominal infections as a Phase IV commitment.

7.2.7 Other Serious Adverse Events

Phase I Studies

No serious adverse events occurred in the Phase I studies.

Phase II and III Studies

Two hundred and twenty-six (226) patients (11.6%) in the ertapenem 1 gm group, 9 patients (14.1%) in the ertapenem 1.5 gm group, 2 patients (6.7%) in the ertapenem 2 gm group, 95 patients (12.3%) in the piperacillin/tazobactam group, and 116 patients (12.3%) in the ceftrixone group had serious clinical adverse experiences occurring during the entire study period. The overall rate of serious adverse experiences in all treatment groups for the period of all study therapy plus follow-up is approximately twice that for the period of parenteral therapy only. Only 22 patients (1.1%) in the ertapenem 1 gm group, 2 patients (0.3%) in the

[11] Draft Guidance for Industry. Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics. July 2001.

piperacillin/tazobactam group, and 6 patients (0.6%) in the ceftriaxone group had serious clinical adverse experiences that were considered drug related. The incidence of serious drug-related clinical adverse experiences for the period of all study therapy plus follow-up in comparison to the period of parenteral therapy only was increased 0.3% in the ertapenem 1 gm group, unchanged in the piperacillin/tazobactam group, and increased 0.4% in the ceftriaxone group.

The following table displays the number (percent) of patients with serious clinical adverse experiences with incidence ≥1% in one or more treatment groups by body system and drug relationship occurring during the entire study (study therapy and follow-up not limited to 14 days).

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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 (Total and Drug Related)

	Ertapenem 1 g (N=1954)[1]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			P/T (N=774)[1]			CTX (N=942)[1]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Patients with one or more adverse experiences	226	(11.6)	22	9	(14.1)	0	2	(6.7)	0	95	(12.3)	2	116	(12.3)	6
Patients with no adverse experience	1728	(88.4)		55	(85.9)		28	(93.3)		679	(87.7)		826	(87.7)	
Body as a Whole/Site Unspecified	**84**	**(4.3)**	**2**	**4**	**(6.3)**	**0**	**0**	**(0.0)**	**0**	**31**	**(4.0)**	**1**	**39**	**(4.1)**	**1**
Death	47 *	(2.4)	0	4	(6.3)	0	0	(0.0)	0	15	(1.9)	0	21	(2.2)	0
Edema/swelling	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Fever	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	1	2	(0.2)	1
Fungemia	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Multiple organ failure	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0
Septicemia	9	(0.5)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	3	(0.3)	0
Shock, septic	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	1	(0.1)	0
Cardiovascular System	**47**	**(2.4)**	**1**	**4**	**(6.3)**	**0**	**0**	**(0.0)**	**0**	**23**	**(3.0)**	**1**	**26**	**(2.8)**	**0**
Arrhythmia	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Asystole	3	(0.2)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Atrial fibrillation	0	(0.0)	0	3	(4.7)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0
Heart failure	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	4	(0.4)	0
Hypotension	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	5	(0.5)	0
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	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Left bundle branch block	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Supraventricular tachycardia	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Thrombosis, deep vein	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0
Ventricular tachycardia	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Digestive System	**51**	**(2.6)**	**8**	**4**	**(6.3)**	**0**	**0**	**(0.0)**	**0**	**33**	**(4.3)**	**0**	**24**	**(2.5)**	**3**
Infection, intra-abdominal	5	(0.3)	0	2	(3.1)	0	0	(0.0)	0	6	(0.8)	0	7	(0.7)	1
Obstruction, intestinal	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0

	Ertapenem 1 g (N=1954)[1]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			P/T (N=774)[1]			CTX (N=942)[1]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Surgery, intestinal, complication	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	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
Endocrine System	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemic and Lymphatic System	8	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	0
Metabolic, Nutritional, Immune	14	(0.7)	0	3	(4.7)	0	0	(0.0)	0	3	(0.4)	0	5	(0.5)	1
Acidosis	3	(0.2)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
BUN increased	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dehydration	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	3	(0.3)	0
Fluid overload	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Musculoskeletal System	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	5	(0.5)	0
Nervous System and Psychiatric Disorder	23	(1.2)	6	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	3	(0.3)	0
Respiratory System	82	(4.2)	1	3	(4.7)	0	2	(6.7)	0	14	(1.8)	0	52	(5.5)	0
Effusion, pleural	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	8	(0.8)	0
Pneumonia	20	(1.0)	1	1	(1.6)	0	2	(6.7)	0	5	(0.6)	0	14	(1.5)	0
Respiratory distress	6	(0.3)	0	2	(3.1)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Skin and Skin Appendage	23	(1.2)	0	0	(0.0)	0	0	(0.0)	0	19	(2.5)	0	0	(0.0)	0
Special Senses	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0

Urogenital System	**32**	**(1.6)**	**3**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**11**	**(1.4)**	**0**	**23**	**(2.4)**	**1**
Infection, urinary tract	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	1
Oliguria/anuria	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Renal insufficiency	7	(0.4)	1	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0

† 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 received metronidazole.

¶ Not including 1 patient whose death was reported in the comments after the 14-day follow-up period.

Entire study includes study therapy and entire follow-up period, not limited to 14 days.

P/T = Piperacillin/tazobactam.

CTX = Ceftriaxone any dose.

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 two 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 E-53, September 21, 2001 submission)

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Medical Officer's Comment: ***Overall, the incidence of drug-related and non-drug-related serious 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 entire study period (study therapy and follow-up not limited to 14 days). Death rates, specifically, were discussed in greater detail in the preceding section.***

7.2.8 Dropouts

Phase I Studies

Clinical adverse experiences that resulted in discontinuation occurred in 11 subjects that received ertapenem. In 10 subjects the discontinuation was determined to be possibly, probably, or definitely study drug related by the investigator. No subject discontinued from the placebo treatment group. Subjects that discontinued from the Phase I studies are displayed in the following table.

Listing of Subjects Who Discontinued Treatment Due to Clinical Adverse Experiences in Phase I Studies

AN	Study Number	Gender	Race	Age (yrs)	Daily Dose of Ertapenem (g)	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Outcome
0057	001004	M	Caucasian	21	3	1	Dizziness	6 min	Mild	Definitely	Recovered
					3		Nausea	51 min	Mild	Definitely	Recovered
					3		Vomiting	1 min	Mild	Definitely	Recovered
					3		Sweating	44 min	Mild	Definitely	Recovered
0043	010004	F	Caucasian	74	Off drug	2	Paresthesia	51 min	Mild	Definitely	Recovered
					1	3	Diarrhea	2 days	Mild	Definitely	Recovered
0030	011004	F	Caucasian	26	0.5	1	Nausea	30 min	Moderate	Probably	Recovered
0021	013004	M	Caucasian	32	1	1	Dizziness	30 min	Moderate	Probably	Recovered
0027	015004	F	Caucasian	27	1	10	Folliculitis	5 days	Mild	Possibly	Recovered
0026	013004	F	Caucasian	40	1	2	Focal abnormality	9 days	Mild	Possibly	Recovered
						4	Reflux esophagitis	6 days	Mild	Possibly	Recovered
0001	019004	M	Caucasian	36	1	15	Pharyngitis	21 days	Moderate	Probably not	Recovered
0006	019004	M	Black	29	Off drug	9	Hoarseness	6 days	Moderate	Probably not	Recovered
0014	019004	M	Black	30	1	2	Urticaria		Moderate	Probably	Ongoing
0023	030004	F	Caucasian	67	1	1	Rash	9 days	Moderate	Probably	Recovered
0024	014004	F	Caucasian	68	Off drug	2	Diarrhea	23 days	Mild	Probably	Recovered
							Rash	4.5 hours	Mild	Possibly	Recovered
							Rash	12.7 hours	Mild	Possibly	Recovered

All subjects received ertapenem including subjects who received ertapenem alone (N=206) and with probenecid (N=141). No subject discontinued from the placebo group.
None of these clinical adverse experiences were serious.

(Applicant's Table E-8, Volume 2 of 22, page E-47)

Phase II and III Studies

During parenteral therapy, clinical adverse experiences that resulted in discontinuation occurred in 86 patients that received ertapenem (82 patients in ertapenem 1 gm group, 3 patients in ertapenem 1.5 gm group, and 1 patients in ertapenem 2 gm group). In 24 patients receiving ertapenem (24 patients in ertapenem 1 gm group, 0 patients in ertapenem 1.5 gm group, and 0 patients in ertapenem 2 gm group) the discontinuation was determined to be possibly, probably, or definitely study drug related by the investigator. During parenteral therapy, clinical adverse experiences that resulted in discontinuation occurred in 76 patients that received comparator agents (40 patients in pipercillin/tazobactam groups and 36 patients in ceftriaxone groups). In 18 patients receiving comparator (12 patients in pipercillin/tazobactam groups and 6 patients in ceftriaxone groups) the discontinuation was determined to be possibly, probably, or definitely study drug related by the investigator.

An additional 45 patients (20 patients in the ertapenem 1 gm group, 1 patient in the ertapenem 1.5 gm group, 1 patient in the ertapenem 2 gm group, 2 patients in the piperacillin/tazobactam group, and 21 patients in the ceftriaxone group) discontinued therapy during the entire study period, but, beyond the parenteral study period. Thirty of these 45 patients discontinued therapy while they were on oral antimicrobial therapy. Of the additional 45 patients that discontinuationed therapy, 18 discontinuations were considered drug related by the investigator (9 patients in the ertapenem 1-g group, 1 patient in the ertapenem 1.5-g group, 1 patient in the piperacillin/tazobactam group, and 7 patients in the ceftriaxone group).

An accounting of patients that discontinued from the Phase II and III studies during the entire study period is displayed in the following table.

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences by Body System During Entire Study–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)[2]			Ceftriaxone (N=942)[3]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Patients with one or more adverse experiences	103	(5.3)	33	4	(6.3)	1	2	(6.7)	0	42	(5.4)	13	57	(6.1)	13
Patients with no adverse experience	1851	(94.7)		60	(93.8)		28	(93.3)		732	(94.6)		885	(93.9)	
Body as a Whole/Site Unspecified	**25**	**(1.3)**	**4**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**11**	**(1.4)**	**1**	**17**	**(1.8)**	**1**
Bacteremia	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cardiopulmonary failure	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Death	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Deterioration, general	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Distention, abdominal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Drug overdose	3	(0.2)	2	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Edema, facial	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	1	(0.1)	0
Fever	6	(0.3)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0
Hyperthermia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Infection, bacterial	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Inflammation	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Multiple organ failure	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Necrosis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pain, abdominal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Reaction, vasovagal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	1
Septicemia	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Shock, septic	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Superinfection	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Syncope	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Unknown cause of death	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
													1	(0.1)	0
Cardiovascular System	**21**	**(1.1)**	**1**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**9**	**(1.2)**	**4**	**8**	**(0.8)**	**1**
Arrhythmia	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Asystole	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
AV block, third degree	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cardiac arrest	6	(0.3)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cardiac tamponade	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cor pulmonale	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
CVA	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Embolism/infarction, pulmonary	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Endocarditis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Gangrene	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Heart failure	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hematoma	0	(0.0)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemorrhage, retroperitoneal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Hemorrhage, subdural	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypertension	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Hypertension, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypotension	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Infused vein complication	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	2	1	(0.1)	0
Myocardial infarction	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Pericarditis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Phlebitis/thrombophlebitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Shock	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Tachycardia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Thrombosis, deep vein	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Digestive System	**15**	**(0.8)**	**9**	**1**	**(1.6)**	**1**	**0**	**(0.0)**	**0**	**8**	**(1.0)**	**3**	**12**	**(1.3)**	**6**
Candidiasis, oral	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cholecystitis	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Diarrhea	3	(0.2)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	3

	Ertapenem 1 g (N=1954)[1c]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[2]			Ceftriaxone (N=942)[1]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Diarrhea, *Clostridium difficile* associated	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dyspepsia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dysphagia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Edema, tongue	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Fistula, abdominal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hepatitis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Ileus	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Impaction, fecal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Infection, intra-abdominal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	1	(0.1)	0
Jaundice	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Nausea	0	(0.0)	0	1	(1.6)	1	0	(0.0)	0	2	(0.3)	2	3	(0.3)	2
Obstruction, intestinal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Peritonitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Stomatitis	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Surgery, intestinal, complication	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Vomiting	2	(0.1)	2	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	3	(0.3)	3
Endocrine System	**1**	**(0.1)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**
Diabetes w/ketoacidosis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemic and Lymphatic System	**1**	**(0.1)**	**1**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**1**	**(0.1)**	**0**
Thrombocytopenia	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Metabolic, Nutritional, Immune	**4**	**(0.2)**	**3**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**2**	**(0.2)**	**2**
Acidosis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Allergy	3	(0.2)	3	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	2
Musculoskeletal System	**4**	**(0.2)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**1**	**(0.1)**	**0**
Fasciitis, necrotizing	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, bone/cartilage	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, joint	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Nervous System and Psychiatric Disorder	**8**	**(0.4)**	**5**	**1**	**(1.6)**	**0**	**0**	**(0.0)**	**0**	**3**	**(0.4)**	**2**	**5**	**(0.5)**	**1**
Anxiety	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Brain disorder	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Confusion	2	(0.1)	1	1	(1.6)	0	0	(0.0)	0	1	(0.1)	1	1	(0.1)	0
Delirium	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dizziness	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypesthesia	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Migraine	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Paresthesia	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Seizure disorder	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Seizure, grand mal	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Somnolence	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Respiratory System	**26**	**(1.3)**	**2**	**0**	**(0.0)**	**0**	**2**	**(6.7)**	**0**	**6**	**(0.8)**	**0**	**17**	**(1.8)**	**1**
Aspiration	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Atelectasis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Bronchitis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Bronchoconstriction	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Chronic obstructive pulmonary disease	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dyspnea	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	1
Edema, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Effusion, pleural	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Empyema	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hoarseness	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Hypoxemia	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Infection, respiratory, lower	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

	Ertapenem 1 g (N=1954)[1,2]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[2]			Ceftriaxone (N=942)[1,3]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
Infiltrate, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Lymphadenopathy, mediastinum	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Neoplasm, lung, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Obstruction, airway	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pneumonia	6	(0.3)	1	0	(0.0)	0	2	(6.7)	0	2	(0.3)	0	4	(0.4)	0
Pneumonia, bacterial	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pneumonia, pneumocystis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Radiodensity, pulmonary	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Respiratory disorder	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Respiratory distress syndrome	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Respiratory failure	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	0
Respiratory insufficiency	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Sepsis, pulmonary	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Tachypnea	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Tuberculosis, pulmonary	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Skin and Skin Appendage	**14**	**(0.7)**	**9**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**9**	**(1.2)**	**6**	**2**	**(0.2)**	**2**
Cellulitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	1	0	(0.0)	0
Infection, skin	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Infection, wound	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, wound, postoperative	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Pruritus	3	(0.2)	3	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Rash	8	(0.4)	7	0	(0.0)	0	0	(0.0)	0	5	(0.6)	5	1	(0.1)	1
Special Senses	**2**	**(0.1)**	**2**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**
Edema, eyelid	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Perversion, taste	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Urogenital System	**5**	**(0.3)**	**2**	**0**	**(0.0)**	**0**	**0**	**(0.0)**	**0**	**2**	**(0.3)**	**0**	**4**	**(0.4)**	**2**
Abortion	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Bleeding, genital	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemorrhage, uterine	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hot flashes	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Infection, pelvic	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Labor abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pregnancy	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pyelonephritis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Renal dysfunction	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Renal insufficiency	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Salpingo-oophoritis	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	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.
DR = Drug related. Number of patients with clinical adverse experiences determined by the investigator to be possibly, probably, or definitely drug related.
N = Number of patients per treatment group.
n = Number of patients reporting clinical adverse experiences.
Entire study includes study therapy and entire follow- up period, not limited to 14 days.

(Table E-56, September 21, 2001 submission)

Medical Officer's Comment: ***In all treatment groups, the drug-related clinical adverse events that led to discontinuation were generally considered of moderate (41/98 patients in the ertapenem 1 gm group, 1/4 patients in the ertapenem 1.5 gm group, 1/2 patients in the ertapenem 2 gm group, 18/42 patients in the piperacillin/tazobactam group, and 23/57 patients in the ceftriaxone group) to severe (50/98 patients in the ertapenem 1 gm group, 1/4 patients in the ertapenem 1.5 gm group, 1/2 patients in the ertapenem 2 gm group, 22/42 patients in the piperacillin/tazobactam group, and 30/57 patients in the ceftriaxone group) intensity by the Investigators.***

The MO agrees with the Applicant's evaluation that there was a similar pattern of adverse experiences and drug-related adverse experiences that limited therapy in the parenteral therapy period and in the entire study period.

7.2.9 Laboratory Findings

Phase I Studies

Laboratory adverse experiences were reported based on the investigator's judgment of its clinical importance. Therefore, a laboratory value outside the normal range may or may not have been considered an adverse experience by the investigator. The percentage of subjects who had laboratory adverse experiences was 4.1% in the ertapenem group and 3.1% in the placebo group. No subject had a serious laboratory adverse experience. No subject discontinued due to a laboratory adverse experience. The number (%) of subjects in the Phase I studies with any laboratory adverse experience are displayed in the following table.

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Number (%) of Subjects With Specific Laboratory Adverse Experiences (Incidence ≥0 % in One or More Treatment Groups) by Laboratory Test Category in Phase I Studies - Total and Drug Related

	MK-0826 (N=220)			Placebo (N=32)		
	n/m*	(%)	[DR/m]	n/m*	(%)	[DR/m]
Subjects with one or more adverse experiences	9/218	(4.1)	[4/218]	1/32	(3.1)	[1/32]
Subjects with no adverse experience	209/218	(95.9)		31/32	(96.9)	
Blood Chemistry	**6/218**	**(2.8)**	**[4/218]**	**1/32**	**(3.1)**	**[1/32]**
Adenovirus ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
ALT increased	6/218	(2.8)	[4/218]	0/32	(0.0)	[0/32]
AST increased	3/218	(1.4)	[1/218]	1/32	(3.1)	[1/32]
Blood urea	0/14	(0.0)	[0/14]	0/0	(0.0)	[0/0]
Blood uric acid	0/40	(0.0)	[0/40]	0/0	(0.0)	[0/0]
BUN	0/99	(0.0)	[0/99]	0/22	(0.0)	[0/22]
Cholesterol	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie a4 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus a10 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus a16 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus a7 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus a9 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b1 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b2 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b3 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b4 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b5 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Coxsackie virus b6 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Direct serum bilirubin	0/101	(0.0)	[0/101]	0/8	(0.0)	[0/8]
Echovirus 11 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Echovirus 16 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Echovirus 30 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Echovirus 4 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Echovirus 9 ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Fasting blood glucose	0/190	(0.0)	[0/190]	0/26	(0.0)	[0/26]
Fasting serum glucose	0/28	(0.0)	[0/28]	0/6	(0.0)	[0/6]
Indirect serum bilirubin	0/6	(0.0)	[0/6]	0/1	(0.0)	[0/1]
Influenza a ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Influenza b ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Mycoplasma pneumon IgG/IgM ab	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Phosphorus (total)	0/14	(0.0)	[0/14]	0/0	(0.0)	[0/0]
Serum albumin	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum alkaline phosphatase	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum beta-hCG	0/14	(0.0)	[0/14]	0/0	(0.0)	[0/0]
Serum bicarbonate	0/162	(0.0)	[0/162]	0/26	(0.0)	[0/26]

Number (%) of Subjects With Specific Laboratory Adverse Experiences (Incidence ≥0 % in One or More Treatment Groups) by Laboratory Test Category in Phase I Studies - Total and Drug Related (cont.)

Serum calcium	0/204	(0.0)	[0/204]	0/32	(0.0)	[0/32]
Serum chloride	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum CO_2	0/30	(0.0)	[0/30]	0/6	(0.0)	[0/6]
Serum creatinine	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum GGT	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Serum LDH	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Serum phosphate	0/12	(0.0)	[0/12]	0/0	(0.0)	[0/0]
Serum phosphorus	0/5	(0.0)	[0/5]	0/0	(0.0)	[0/0]
Serum potassium	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum sodium	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Serum urea	0/105	(0.0)	[0/105]	0/10	(0.0)	[0/10]
Total serum bilirubin	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Total serum protein	0/134	(0.0)	[0/134]	0/10	(0.0)	[0/10]
Triglycerides	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Hematology	**3/218**	**(1.4)**	**[0/218]**	**0/32**	**(0.0)**	**[0/32]**
Band neutrophils	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Basophils	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Eosinophils	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Erythrocyte count	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Hematocrit	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Hemoglobin decreased	2/218	(0.9)	[0/218]	0/32	(0.0)	[0/32]
Lymphocytes	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Metamyelocytes	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Monocytes	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Mononucleosis test	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Myelocytes	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Neutrophils	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
Platelet count decreased	1/218	(0.5)	[0/218]	0/32	(0.0)	[0/32]
Segmented neutrophils	0/218	(0.0)	[0/218]	0/32	(0.0)	[0/32]
WBC decreased	1/218	(0.5)	[0/218]	0/32	(0.0)	[0/32]
Urinalysis	**0/211**	**(0.0)**	**[0/211]**	**0/32**	**(0.0)**	**[0/32]**
Epithelial cells	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Granular casts	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Hyaline casts	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine beta-hCG	0/8	(0.0)	[0/8]	0/0	(0.0)	[0/0]
Urine bilirubin	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine casts	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine crystals	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine glucose	0/211	(0.0)	[0/211]	0/32	(0.0)	[0/32]
Urine nitrate	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Urine pH	0/211	(0.0)	[0/211]	0/32	(0.0)	[0/32]
Urine protein	0/211	(0.0)	[0/211]	0/32	(0.0)	[0/32]

Number (%) of Subjects With Specific Laboratory Adverse Experiences (Incidence ≥0 % in One or More Treatment Groups) by Laboratory Test Category in Phase I Studies - Total and Drug Related (cont.)

Urine RBCs	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine urobilinogen	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Urine WBCs	0/192	(0.0)	[0/192]	0/27	(0.0)	[0/27]
Miscellaneous	0/5	(0.0)	[0/5]	0/0	(0.0)	[0/0]
C. difficile	0/5	(0.0)	[0/5]	0/0	(0.0)	[0/0]
Miscellaneous	0/30	(0.0)	[0/30]	0/6	(0.0)	[0/6]
Urine hCG	0/30	(0.0)	[0/30]	0/6	(0.0)	[0/6]
Miscellaneous	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Adenovirus detection	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Influenza culture	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Legionella culture	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]

N= Total number of subjects per treatment group.

* n/m = Number of subjects with laboratory adverse experience/number of subjects with laboratory test.

n: Number of subjects reporting laboratory adverse experiences.

[DR/m]: Number of subjects reporting lab adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related/number of subjects with laboratory test.

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 categories are listed in which at least 1 subject had an adverse experience.

(Applicant's Reference 81, clinstat/other/0081.pdf)

Medical Officer's Comment: ***The most common laboratory adverse experiences in subjects receiving ertapenem were increases in ALT in 6 of 218 subjects (2.8%) and increases in AST in 3 of 218 subjects (1.4%). Only 1 of the 32 subjects (3.1%) who received placebo had a laboratory adverse experience (increased AST). The most common drug-related laboratory adverse experience in subjects receiving ertapenem was increased ALT (1.8%). In an exploratory evaluation, the Applicant assessed the change from pretreatment baseline values in selected laboratory parameters. Only ALT and, to a lesser extent, AST showed a small but consistent increase in mean value, although still within the normal range. The mean increase in ALT on Day 8 of dosing in healthy young volunteers ranged from 8 to 28 U/L across the dose levels. These findings suggest that increases in ALT and to a lesser extent AST may be associated with administration of ertapenem.***

The Applicant also assessed the occurence of predefined clinically significant laboratory abnormalities (CSLAs) for specified tests for subjects whose most abnormal laboratory value represented a worsening from baseline. In order to be considered in the population for CSLAs, subjects had to have a baseline laboratory value, at least 1 postbaseline laboratory test, and have normal ranges in the database. For neutrophil counts, the clinical pharmacology studies had a normal range for WBC count and for the percentage of neutrophils. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin, the CSLA criteria were defined in terms of a fixed bound. For total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, and serum creatinine, the CSLA criteria were defined in terms of exceeding a predefined multiple of the ULN. The following table displays the CSLAs for subjects in the Phase I studies.

Number (%) of Subjects With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group in Phase I Studies

Laboratory Test	CSLA Criteria	Ertapenem† (N=220)		Placebo (N=32)	
		n/m‡	%	n/m	%
Absolute neutrophils (ths/mm³)	<1.8	26/218	11.9	3/32	9.4
	<1	3/218	1.4	0/32	0.0
Serum alkaline phosphatase (U/L)	>2.5 x ULN	1/218	0.5	0/32	0.0
	>5 x ULN	0/218	0.0	0/32	0.0
ALT (U/L)	>2.5 x ULN	1/218	0.5	0/32	0.0
	>5 x ULN	0/218	0.0	0/32	0.0
AST (U/L)	>2.5 x ULN	0/218	0.0	0/32	0.0
	>5 x ULN	0/218	0.0	0/32	0.0
Total serum bilirubin (mg/dL)	>1.5 x ULN	5/218	2.3	1/32	3.1
	>2.5 x ULN	0/218	0.0	0/32	0.0
Direct serum bilirubin (mg/dL)	>1.5 x ULN	3/84	3.6	0/5	0.0
	>2.5 x ULN	0/84	0.0	0/5	0.0
Serum creatinine (mg/dL)	>1.5 x ULN	11/218	5.0	0/32	0.0
	>3 x ULN	8/218	3.7	0/32	0.0
Hemoglobin (gm/dL)	<8	1/218	0.5	0/32	0.0
Hematocrit (%)	<24	1/218	0.5	0/32	0.0
Platelet count (ths/mm³)	<75	0/218	0.0	0/32	0.0

† Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).
‡ n/m = Number of subjects with laboratory abnormality/number of subjects with laboratory test.
ULN = Upper limit of normal.

(Applicant's Table E-14, Volume 2 of 22, page E-57)

Medical Officer's Comment: ***The 26 subjects (11.9%) that received ertapenem and 3 subjects (9.4%) that received placebo developed absolute neutrophil counts <1800 THS/mm³; these subjects were distributed between the single- and multiple-dose studies. The baseline (predose Day 1) absolute neutrophil count in 22 of 26 ertapenem subjects was <2500 THS/mm³. Based on the analysis submitted by the Applicant on November 15, 2001, there was no clear relationship between ertapenem dose or duration of ertapenem administration and decrease in absolute neutrophil count. Based on the Medical Officer's review of these patients, there also did not appear to be a clear relationship between gender, race, or weight. Three subjects that received ertapenem had absolute neutrophil counts that transiently fell below 1000 THS/mm³ but not below 500 THS/mm³. In one of these three subjects the ANC < 1000 THS/mm³ actually occurred predose and increased to > 1000 THS/mm³ postdose.***

Three ertapenem subjects developed direct bilirubin elevations between 1.5x ULN and 2.5x ULN that were transient. One of the three subjects had associated elevations of AST and ALT that were less than 2x ULN for these parameters.

The 11 ertapenem subjects with elevated creatinine values were enrolled in the renal insufficiency study and these elevations were consistent with their baseline pattern of elevated creatinine.

Phase II and III Studies

Laboratory adverse experiences were reported based on the investigator's judgment of its clinical importance. Therefore, a laboratory value outside the normal range may or may not have been considered an adverse experience by the investigator. The percentage of subjects who had laboratory adverse experiences during the parenteral period was 23.8% in the ertapenem 1 gm group, 28.3% in the piperacillin/tazobactam group, and 19.3% in the ceftriaxone group. The percentage of subjects who had laboratory adverse experiences during the parenteral period plus 14-day follow-up period (including studies for which an oral follow-up therapy was allowed) was 28.3% in the ertapenem 1 gm group, 31.0% in the piperacillin/tazobactam group, and 24.8% in the ceftriaxone group. The following table displays the number (percent) of all patients who received at least 1 dose of study therapy with laboratory adverse experiences during the parenteral therapy period and during the parenteral therapy period plus 14 day safety follow-up period.

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ON ORIGINAL

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ON ORIGINAL

Laboratory Adverse Experience Summary by Treatment Group

Number (%) of patients	Ertapenem 1 g (N=1850)†‡		Ertapenem 1.5 g (N=60)		Ertapenem 2 g (N=30)		P/T (N=750)†		CTX (N=900)‡§		P/T + CTX (N=1650)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Parenteral Therapy Period												
With one or more adverse experiences	440	(23.8)	26	(43.3)	5	(16.7)	212	(28.3)	174	(19.3)	386	(23.4)
With no adverse experience	1410	(76.2)	34	(56.7)	25	(83.3)	538	(71.7)	726	(80.7)	1264	(76.6)
With drug-related adverse experiences%	225	(12.2)	5	(8.3)	1	(3.3)	105	(14.0)	79	(8.8)	184	(11.2)
With serious adverse experience	17	(0.9)	1	(1.7)	0	(0.0)	11	(1.5)	6	(0.3)	17	(1.0)
With serious drug-related adverse experience	12	(0.6)	0	(0.0)	0	(0.0)	4	(0.5)	4	(0.4)	8	(0.5)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	6	(0.3)	0	(0.0)	0	(0.0)	4	(0.5)	3	(0.3)	7	(0.4)
Discontinued due to a drug-related adverse experience	3	(0.2)	0	(0.0)	0	(0.0)	3	(0.4)	1	(0.1)	4	(0.2)
Discontinued due to a serious adverse experience	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious drug-related adverse experience	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Parenteral Period and 14-Day Follow-Up Period												
	N=1887		N=62		N=30		N=756		N=920		N=1676	
with one or more adverse experiences	534	(28.3)	27	(43.5)	7	(23.3)	234	(31.0)	228	(24.8)	462	(27.6)
with no adverse experience	1353	(71.7)	35	(56.5)	23	(76.7)	522	(69.0)	692	(75.2)	1214	(72.4)
with drug-related adverse experiences%	260	(13.8)	5	(8.1)	2	(6.7)	113	(14.9)	99	(10.8)	212	(12.6)
with serious adverse experiences	21	(1.1)	1	(1.6)	0	(0.0)	11	(1.5)	9	(1.0)	20	(1.2)
with serious drug-related adverse experiences	13	(0.7)	0	(0.0)	0	(0.0)	4	(0.5)	6	(0.7)	10	(0.6)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	6	(0.3)	0	(0.0)	0	(0.0)	4	(0.5)	3	(0.3)	7	(0.4)
discontinued due to a drug-related adverse experience	3	(0.2)	0	(0.0)	0	(0.0)	3	(0.4)	1	(0.1)	4	(0.2)
discontinued due to a serious adverse experience	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† 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: Applicant's Tables E-39, E-50, E-51, E-53, E-56, and E-57 in the original NDA submission and Tables 27, 38, *in the July 3, 2001 submission to the NDA)

Medical Officer's Comment: ***Overall the rates of rate of both drug-related and non-drug-related laboratory adverse events and drug-related laboratory adverse events by were similar between the ertapenem 1 gm group and combined comparator group.***

The following table displays the number (percent) of patients with investigator-reported specific laboratory adverse experiences with an incidence ≥1% in one or more treatment groups by laboratory test category occurring during the study therapy and 14-day follow-up period.

Number (%) of Patients With Specific Laboratory Adverse Experiences
(Incidence ≥1 % in One or More Treatment Groups) by Laboratory Test Category
During Study Therapy And 14-Day Follow-Up Period—
All Clinical Studies
(Total and Drug Related)

	Ertapenem 1 g (N=1954)			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)			Ceftriaxone (N=942)		
	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]
Patients with one or more adverse experiences	534/1888	(28.3)	[260/1888]	27/62	(43.5)	[5/62]	7/30	(23.3)	[2/30]	234/755	(31.0)	[113/755]	229/920	(24.9)	[106/920]
Patients with no adverse experience	1354/1888	(71.7)		35/62	(56.5)		23/30	(76.7)		521/755	(69.0)		691/920	(75.1)	
Blood Chemistry	**341/1867**	**(18.3)**	**[173/1867]**	**21/61**	**(34.4)**	**[5/61]**	**0/30**	**(0.0)**	**[0/30]**	**154/748**	**(20.6)**	**[64/748]**	**153/906**	**(16.9)**	**[78/906]**
Acidosis	1/1	(100)	[1/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
ALT increased	147/1736	(8.5)	[105/1736]	9/48	(18.8)	[3/48]	0/29	(0.0)	[0/29]	50/685	(7.3)	[30/685]	57/827	(6.9)	[42/827]
Amylase increased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	2/2	(100)	[0/2]	0/0	(0.0)	[0/0]
ANA positive	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Arterial pH decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]
Arterial pO_2 decreased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
AST increased	178/1813	(9.8)	[99/1813]	9/55	(16.4)	[4/55]	0/29	(0.0)	[0/29]	60/726	(8.3)	[33/726]	56/866	(6.5)	[37/866]
Blood urea increased	3/182	(1.6)	[0/182]	0/0	(0.0)	[0/0]	0/20	(0.0)	[0/20]	4/69	(5.8)	[0/69]	2/106	(1.9)	[1/106]
BUN increased	12/1619	(0.7)	[3/1619]	3/45	(6.6)	[0/45]	0/10	(0.0)	[0/10]	7/664	(1.1)	[3/664]	12/766	(1.6)	[3/766]
Direct serum bilirubin increased	16/1136	(1.4)	[8/1136]	4/30	(13.3)	[2/30]	0/24	(0.0)	[0/24]	7/491	(1.4)	[2/491]	2/516	(0.4)	[0/516]
Hemoglobin increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
HIV positive	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Indirect serum bilirubin increased	11/888	(1.2)	[5/888]	0/5	(0.0)	[0/5]	0/8	(0.0)	[0/8]	1/381	(0.3)	[1/381]	3/374	(0.8)	[3/374]
Ionized calcium decreased	0/0	(0.0)	[0/0]	0/2	(0.0)	[0/2]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]
Lipase decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]
Lipase increased	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Oxygen saturation decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
PCO_2 increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Prostate specific antigen increased	2/2	(100)	[0/2]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Serum albumin decreased	22/1775	(1.2)	[0/1775]	4/55	(7.3)	[0/55]	0/27	(0.0)	[0/27]	11/717	(1.5)	[1/717]	14/866	(1.6)	[0/866]
Serum alkaline phosphatase increased	94/1808	(5.2)	[62/1808]	7/54	(13.0)	[3/54]	0/28	(0.0)	[0/28]	52/722	(7.2)	[29/722]	24/871	(2.8)	[13/871]
Serum bicarbonate decreased	6/1536	(0.4)	[1/1536]	1/54	(1.9)	[0/54]	0/21	(0.0)	[0/21]	3/629	(0.5)	[0/629]	2/757	(0.3)	[0/757]
Serum calcium decreased	7/1770	(0.4)	[0/1770]	2/58	(3.4)	[0/58]	0/28	(0.0)	[0/28]	2/713	(0.3)	[0/713]	7/866	(0.8)	[0/866]
Serum chloride increased	2/1792	(0.1)	[0/1792]	1/61	(1.6)	[0/61]	0/29	(0.0)	[0/29]	1/724	(0.1)	[0/724]	2/873	(0.2)	[0/873]
Serum cholesterol inc	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]
Serum CO_2 decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Serum CPK decreased	0/86	(0.0)	[0/86]	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/30	(3.3)	[0/30]
Serum CPK increased	22/86	(25.6)	[11/86]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	6/30	(20.0)	[2/30]
Serum creatinine increased	18/1855	(1.0)	[3/1855]	3/60	(5.0)	[0/60]	0/30	(0.0)	[0/30]	20/741	(2.7)	[4/741]	11/901	(1.2)	[3/901]
Serum GGT increased	1/1	(100)	[1/1]	1/1	(100)	[1/1]	0/0	(0.0)	[0/0]	3/3	(100)	[3/3]	2/2	(100)	[0/2]
Serum glucose decreased	13/1852	(0.7)	[0/1852]	1/61	(1.6)	[0/61]	0/30	(0.0)	[0/30]	4/743	(0.5)	[1/743]	2/897	(0.2)	[0/897]
Serum glucose increased	28/1852	(1.5)	[3/1852]	2/61	(3.3)	[0/61]	0/30	(0.0)	[0/30]	17/743	(2.3)	[1/743]	18/897	(2.0)	[2/897]
Serum iron decreased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[1/1]	0/0	(0.0)	[0/0]
Serum LDH increased	4/4	(100)	[2/4]	1/1	(100)	[1/1]	0/0	(0.0)	[0/0]	1/1	(100)	[1/1]	3/3	(100)	[1/3]
Serum magnesium decreased	2/2	(100)	[0/2]	3/3	(100)	[0/3]	0/0	(0.0)	[0/0]	3/3	(100)	[0/3]	2/2	(100)	[0/2]
Serum magnesium increased	1/2	(50.0)	[0/2]	0/3	(0.0)	[0/3]	0/0	(0.0)	[0/0]	0/3	(0.0)	[0/3]	0/2	(0.0)	[0/2]
Serum phosphate decreased	1/2	(50.0)	[0/2]	2/3	(66.7)	[0/3]	0/0	(0.0)	[0/0]	2/2	(100)	[0/2]	5/6	(83.3)	[2/6]
Serum phosphorus increased	1/2	(50.0)	[1/2]	0/3	(0.0)	[0/3]	0/0	(0.0)	[0/0]	0/2	(0.0)	[0/2]	1/6	(16.7)	[0/6]
Serum potassium decreased	33/1856	(1.8)	[3/1856]	2/61	(3.3)	[0/61]	0/30	(0.0)	[0/30]	21/745	(2.8)	[0/745]	22/905	(2.4)	[2/905]
Serum potassium increased	16/1856	(0.9)	[2/1856]	1/61	(1.6)	[0/61]	0/30	(0.0)	[0/30]	4/745	(0.5)	[0/745]	6/905	(0.7)	[0/905]
Serum pseudoanemia decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Serum sodium decreased	5/1857	(0.3)	[0/1857]	1/61	(1.6)	[0/61]	0/30	(0.0)	[0/30]	2/745	(0.3)	[0/745]	3/904	(0.6)	[0/904]

	Ertapenem 1 g (N=1954)*			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)†			Ceftriaxone (N=942)‡		
	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]	n/m	(%)	[DR/m]
Serum sodium increased	5/1857	(0.3)	[1/1857]	1/61	(1.6)	[1/61]	0/30	(0.0)	[0/30]	0/745	(0.0)	[0/745]	3/904	(0.3)	[3/904]
Serum uric acid increased	1/2	(50.0)	[0/2]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	½	(50.0)	[0/2]
Serum uric acid increased	1/2	(50.0)	[1/2]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/1	(0.0)	[0/1]	½	(50.0)	[0/2]
Thyroid function abnormal	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Total serum bilirubin increased	30/1809	(1.7)	[9/1809]	7/53	(13.2)	[2/53]	0/29	(0.0)	[0/29]	10/722	(1.4)	[4/722]	30/872	(3.4)	[5/872]
Total serum protein decreased	11/1772	(0.6)	[0/1772]	2/54	(3.7)	[0/54]	0/28	(0.0)	[0/28]	10/697	(1.4)	[0/697]	10/864	(1.2)	[0/864]
Triglycerides increased	2/2	(100)	[1/2]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
TSH increased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Hematology	**275/1882**	**(14.6)**	**[111/1882]**	**16/62**	**(25.8)**	**[1/62]**	**6/30**	**(20.0)**	**[2/30]**	**116/752**	**(15.4)**	**[57/752]**	**114/913**	**(12.5)**	**[44/913]**
Basal neutrophils increased	3/1830	(0.2)	[1/1830]	1/57	(1.8)	[0/57]	0/30	(0.0)	[0/30]	1/717	(0.1)	[0/717]	2/893	(0.2)	[0/893]
CD_4 count decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Eosinophils increased	31/1830	(1.7)	[20/1830]	0/57	(0.0)	[0/57]	1/30	(3.3)	[1/30]	8/717	(1.1)	[5/717]	16/893	(1.8)	[13/893]
ESR increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]
Fibrinogen increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Hematocrit decreased	61/1877	(3.2)	[7/1877]	9/62	(14.5)	[0/62]	0/30	(0.0)	[0/30]	22/748	(2.9)	[2/748]	22/911	(2.4)	[0/911]
Hemoglobin decreased	87/1877	(4.6)	[8/1877]	10/62	(16.1)	[0/62]	1/30	(3.3)	[0/30]	35/748	(4.7)	[2/748]	32/911	(3.5)	[1/911]
INR increased	3/1393	(0.2)	[0/1393]	0/13	(0.0)	[0/13]	0/13	(0.0)	[0/13]	7/638	(1.1)	[3/638]	0/606	(0.0)	[0/606]
Lymphocytes decreased	1/1830	(0.1)	[1/1830]	1/57	(1.8)	[0/57]	0/30	(0.0)	[0/30]	2/717	(0.3)	[0/717]	4/893	(0.4)	[1/893]
MCV increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Monocytes decreased	1/1830	(0.1)	[0/1830]	1/57	(1.8)	[0/57]	0/30	(0.0)	[0/30]	0/717	(0.0)	[0/717]	1/893	(0.1)	[0/893]
Platelet count decreased	20/1874	(1.1)	[0/1874]	5/62	(8.1)	[1/62]	1/30	(3.3)	[0/30]	9/744	(1.2)	[3/744]	9/909	(1.0)	[5/909]
Platelet count increased	97/1874	(5.2)	[52/1874]	3/62	(4.8)	[0/62]	1/30	(3.3)	[0/30]	47/744	(6.3)	[34/744]	32/909	(3.5)	[8/909]
Prothrombin time increased	11/1682	(0.7)	[1/1682]	0/46	(0.0)	[0/46]	0/18	(0.0)	[0/18]	14/683	(2.0)	[0/683]	7/813	(0.9)	[2/813]
PTT increased	14/1600	(0.9)	[6/1600]	1/34	(2.9)	[0/34]	0/28	(0.0)	[0/28]	16/695	(2.3)	[6/695]	8/811	(1.0)	[2/811]
RBC count decreased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
RDW, increased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Schistocytosis	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Segmented neutrophils decreased	23/1830	(1.3)	[16/1830]	0/57	(0.0)	[0/57]	2/30	(6.7)	[1/30]	2/717	(0.3)	[1/717]	7/893	(0.8)	[6/893]
Segmented neutrophils increased	120/1830	(6.6)	[2/1830]	2/57	(3.5)	[0/57]	0/30	(0.0)	[0/30]	6/717	(0.8)	[0/717]	6/893	(0.7)	[0/893]
Teardrop cells	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
WBC decreased	23/1876	(1.2)	[16/1876]	1/62	(1.6)	[0/62]	0/30	(0.0)	[0/30]	5/748	(0.7)	[3/748]	13/911	(1.4)	[6/911]
WBC increased	35/1876	(1.9)	[2/1876]	6/62	(9.7)	[0/62]	0/30	(0.0)	[0/30]	25/748	(3.3)	[1/748]	13/911	(1.4)	[1/911]
Urinalysis	**93/1762**	**(5.3)**	**[23/1762]**	**4/52**	**(7.7)**	**[0/52]**	**0/26**	**(0.0)**	**[0/26]**	**46/693**	**(6.6)**	**[15/693]**	**32/850**	**(3.7)**	**[9/850]**
Creatinine clearance decreased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	2/2	(100)	[0/2]	0/0	(0.0)	[0/0]
Urine bacteria increased	26/1641	(1.6)	[6/1641]	1/50	(2.0)	[0/50]	0/26	(0.0)	[0/26]	9/627	(1.4)	[1/627]	10/835	(1.2)	[2/835]
Urine blood increased	8/1630	(0.5)	[1/1630]	1/48	(2.1)	[0/48]	0/26	(0.0)	[0/26]	5/627	(0.8)	[0/627]	0/830	(0.0)	[0/830]
Urine protein increased	12/1725	(0.7)	[0/1725]	1/52	(1.9)	[0/52]	0/25	(0.0)	[0/25]	8/685	(1.2)	[2/685]	7/836	(0.8)	[2/836]
Urine RBC's increased	27/1641	(1.6)	[3/1641]	2/50	(4.0)	[0/50]	0/26	(0.0)	[0/26]	18/627	(2.9)	[4/627]	8/835	(1.0)	[1/835]
Urine transitional cells increased	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Urine trichomonas	0/1	(0.0)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	1/1	(100)	[1/1]
Urine WBC's increased	32/1641	(2.0)	[4/1641]	2/50	(4.0)	[0/50]	0/26	(0.0)	[0/26]	20/627	(3.2)	[4/627]	9/835	(1.1)	[1/835]
Urine yeast present	8/1641	(0.5)	[2/1641]	1/50	(2.0)	[0/50]	0/26	(0.0)	[0/26]	4/627	(0.6)	[3/627]	3/835	(0.4)	[2/835]
Urine yeast, nonfilamentic	4/4	(100)	[4/4]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[1/1]
Urine 24 hr urea increased	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]
Miscellaneous	**9/11**	**(81.8)**	**[6/11]**	**0/1**	**(0.0)**	**[0/1]**	**1/1**	**(100)**	**[0/1]**	**2/3**	**(66.7)**	**[1/3]**	**4/4**	**(100)**	**[2/4]**
Clostridium difficile toxin, positive	7/10	(70.0)	[6/10]	0/1	(0.0)	[0/1]	1/1	(100)	[0/1]	1/2	(50.0)	[1/2]	4/4	(100)	[2/4]
Fecal occult blood	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]
Gastric positive	1/1	(100)	[0/1]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]	0/0	(0.0)	[0/0]

† 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/m = Number of patients with laboratory adverse experience/number of treated patients with at least one laboratory test post-baseline.

(DR/m) = Number of patients reporting laboratory adverse experiences determined by the investigator to be possibly, probably, or definitely drug related/number of patients with the laboratory test.

Although a patient may have had two 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.

(Table E-60, September 21, 2001 submission)

Medical Officer's Comment: ***In the parenteral period plus 14-day follow-up period, the rate of both drug-related and non-drug-related laboratory adverse events and drug-related laboratory adverse events by specific laboratory test were similar between the ertapenem 1 gm group and combined comparator group. The most common laboratory adverse experiences were increased ALT (8.5% ertapenem 1 gm group and 7.1% combined piperacillin/tazobactam + ceftriaxone group), AST (7.6% ertapenem 1 gm group and 7.3% combined piperacillin/tazobactam + ceftriaxone group), increased alkaline***

phosphatase (5.2% ertapenem 1 gm group and 4.8% combined piperacillin/tazobactam + ceftriaxone group), and increased platelet count (5.2% ertapenem 1 gm group and 4.8% combined piperacillin/tazobactam + ceftriaxone group).

The rates of adverse laboratory events were also similar, although with slightly lower rates, when values for the parenteral therapy only period were reviewed.

The following table displays the number (percent) of patients with serious laboratory adverse experiences with an incidence ≥1% in one or more treatment groups by laboratory test category occurring during entire study period (study therapy and entire follow-up period, not limited to 14 days). Of the 3764 treated patients with a laboratory test during the entire study period, 24 (1.3%) in the ertapenem 1 gm group, 1 (1.6%) in the ertapenem 1.5 gm group, 0 (0.0%) in the ertapenem 2 gm group, 12 (1.6%) in the piperacillin/tazobactam group, and 10 (1.1%) in the ceftriaxone group had a serious laboratory adverse experience during the entire study.

Number (%) of Patients With Serious Laboratory Adverse Experiences (Incidence ≥1 % in One or More Treatment Groups) by Laboratory Test Category During Entire Study—All Clinical Studies (Total and Drug Related)

	Ertapenem 1 gm (N=1954)[†‡]			Ertapenem 1.5 gm (N=64)			Ertapenem 2 gm (N=30)			Piperacillin/Tazobactam (N=774)[†]			Ceftriaxone (N=942)[‡§]		
	n/m	(%)	DR/m	n/m	(%)	DR/m	n/m	(%)	DR/m	n/m	(%)	DR/m	n/m	(%)	DR/m
Patients with one or more adverse experiences	24/1898	(1.3)	15/1898	1/62	(1.6)	0/62	0/30	(0.0)	0/30	12/757	(1.6)	5/757	10/922	(1.1)	6/922
Patients with no adverse experience	1874/1898	(98.7)		61/62	(98.4)		30/30	(100)		745/757	(98.4)		912/922	(98.9)	
Blood Chemistry	**16/1882**	**(0.9)**	**12/1882**	**1/61**	**(1.6)**	**0/61**	**0/30**	**(0.0)**	**0/30**	**6/753**	**(0.8)**	**2/753**	**5/911**	**(0.5)**	**4/911**
Blood urea increased	0/182	(0.0)	0/182	0/0	(0.0)	0/0	0/20	(0.0)	0/20	2/69	(2.9)	0/69	0/107	(0.0)	0/107
BUN increased	1/1637	(0.1)	0/1637	1/61	(1.6)	0/61	0/10	(0.0)	0/10	0/672	(0.0)	0/672	0/769	(0.0)	0/769
HIV positive	1/1	(100)	0/1	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0
Serum bicarbonate decreased	1/1550	(0.1)	0/1550	1/54	(1.9)	0/54	0/21	(0.0)	0/21	0/634	(0.0)	0/634	0/762	(0.0)	0/762
Serum creatinine increased	2/1873	(0.1)	1/1873	1/61	(1.6)	0/61	0/30	(0.0)	0/30	4/751	(0.5)	1/751	0/906	(0.0)	0/906
Serum LDH increased	0/4	(0.0)	0/4	0/1	(0.0)	0/1	0/0	(0.0)	0/0	0/1	(0.0)	0/1	1/3	(33.3)	1/3
Serum magnesium decreased	0/3	(0.0)	0/3	0/3	(0.0)	0/3	0/0	(0.0)	0/0	1/3	(33.3)	0/3	0/2	(0.0)	0/2
Hematology	**10/1894**	**(0.5)**	**4/1894**	**1/62**	**(1.6)**	**0/62**	**0/30**	**(0.0)**	**0/30**	**6/755**	**(0.8)**	**3/755**	**3/916**	**(0.3)**	**1/916**
CD4 count decreased	1/1	(100)	0/1	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0
WBC increased	0/1890	(0.0)	0/1890	1/62	(1.6)	0/62	0/30	(0.0)	0/30	1/754	(0.1)	0/754	0/915	(0.0)	0/915
Miscellaneous	**1/12**	**(8.3)**	**0/12**	**0/1**	**(0.0)**	**0/1**	**0/1**	**(0.0)**	**0/1**	**0/3**	**(0.0)**	**0/3**	**1/4**	**(25.0)**	**1/4**
Clostridium difficile toxin, positive	1/11	(9.1)	0/11	0/1	(0.0)	0/1	0/1	(0.0)	0/1	0/2	(0.0)	0/2	1/4	(25.0)	1/4
Urinalysis	**0/1794**	**(0.0)**	**0/1794**	**1/53**	**(1.9)**	**0/53**	**0/28**	**(0.0)**	**0/28**	**2/716**	**(0.3)**	**0/716**	**1/866**	**(0.1)**	**0/866**
Bladder tumor antigen increased	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	1/1	(100)	0/1
Creatinine clearance decreased	0/0	(0.0)	0/0	0/0	(0.0)	0/0	0/0	(0.0)	0/0	2/2	(100)	0/2	0/0	(0.0)	0/0
Urine blood increased	0/1684	(0.0)	0/1684	1/49	(2.0)	0/49	0/28	(0.0)	0/28	0/647	(0.0)	0/647	0/837	(0.0)	0/837
Urine RBC's increased	0/1674	(0.0)	0/1674	1/51	(2.0)	0/51	0/28	(0.0)	0/28	0/647	(0.0)	0/647	0/845	(0.0)	0/845

† 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 = Total number of patients per treatment group.
n/m = Number of patients with laboratory adverse experience/ number of patients with laboratory test.
DR/m= Number of patients reporting laboratory adverse experiences, determined by the investigator to be possibly, probably, or definitely drug related/ number of patients with laboratory test.
Entire study includes study therapy and entire follow-up period, not limited to 14 days. Although a patient may have had 2 or more serious 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 serious adverse experience.

(Table 62, September 21, 2001 submission)

Medical Officer's Comment: ***In the entire study period, the rate of both drug-related and non-drug-related serious laboratory adverse events were similar between the ertapenem 1 gm group and combined comparator group.***

The following table displays the number (percent) of patients with specific drug-related laboratory advesre events with an incidence ≥1% that occurred during the study therapy plus 14-day follow-up period.

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥1 % in One or More Treatment Groups) by Laboratory Test Category During Study Therapy And 14-Day Follow-Up Period—All Clinical Studies (Drug Related)

	Ertapenem 1 g (N=1954)†‡		Piperacillin/Tazobactam (N=774)†		Ceftriaxone (N=942)‡§		Piperacillin/Tazobactam + Ceftriaxone (N=1716)	
	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more drug-related adverse experiences*	260/1888	(13.8)	113/755	(15.0)	106/920	(11.5)	219/1675	(13.1)
Patients with no drug-related adverse experience	1628/1888	(86.2)	642/755	(85.0)	814/920	(88.5)	1456/1675	(86.9)
Blood Chemistry	**172/1867**	**(9.2)**	**64/748**	**(8.6)**	**70/906**	**(7.7)**	**134/1654**	**(8.1)**
Acidosis	1/1	(100)	0/0	(0.0)	0/0	(0.0)	0/0	(0.0)
ALT increased	105/1736	(6.0)	30/685	(4.4)	42/827	(5.1)	72/1512	(4.8)
AST increased	95/1813	(5.2)	33/726	(4.5)	37/866	(4.3)	70/1592	(4.4)
Direct serum bilirubin increased	8/1136	(0.7)	2/491	(0.4)	0/516	(0.0)	2/1007	(0.2)
Serum alkaline phosphatase increased	62/1808	(3.4)	29/722	(4.0)	13/871	(1.5)	42/1593	(2.6)
Serum CPK increased	11/86	(12.8)	0/0	(0.0)	2/30	(6.7)	2/30	(6.7)
Serum GGT increased	1/1	(100)	3/5	(60.0)	0/2	(0.0)	3/7	(42.9)
Serum iron decreased	0/0	(0.0)	1/1	(100)	0/0	(0.0)	1/1	(100)
Serum LDH increased	2/4	(50.0)	1/1	(100)	1/3	(33.3)	2/4	(50.0)
Serum phosphate decreased	0/2	(0.0)	0/2	(0.0)	2/6	(33.3)	2/8	(25.0)
Serum phosphorus increased	1/2	(50.0)	0/2	(0.0)	0/6	(0.0)	0/8	(0.0)
Serum uric acid increased	1/2	(50.0)	0/1	(0.0)	0/2	(0.0)	0/3	(0.0)
Total serum bilirubin increased	9/1809	(0.5)	4/722	(0.6)	5/872	(0.6)	9/1594	(0.6)
Triglycerides increased	1/2	(50.0)	0/0	(0.0)	0/0	(0.0)	0/0	(0.0)
Hematology	**111/1882**	**(5.9)**	**57/752**	**(7.6)**	**44/912**	**(4.8)**	**101/1664**	**(6.1)**
Eosinophils increased	20/1830	(1.1)	5/717	(0.7)	13/893	(1.5)	18/1610	(1.1)
ESR increased	0/1	(0.0)	0/0	(0.0)	1/1	(100)	1/1	(100)
Platelet count decreased	9/1874	(0.5)	3/744	(0.4)	5/909	(0.6)	8/1653	(0.5)
Platelet count increased	52/1874	(2.8)	34/744	(4.6)	8/909	(0.9)	42/1653	(2.5)
Prothrombin time increased	1/1682	(0.1)	9/683	(1.3)	2/813	(0.2)	11/1496	(0.7)
Segmented neutrophils decreased	16/1830	(0.9)	1/717	(0.1)	6/893	(0.7)	7/1610	(0.4)
Urinalysis	**23/1762**	**(1.3)**	**15/693**	**(2.2)**	**9/859**	**(1.0)**	**24/1552**	**(1.5)**
Urine trichomonas	0/1	(0.0)	0/1	(0.0)	1/1	(100)	1/2	(50.0)
Urine yeast, non-diagnostic	4/4	(100)	0/0	(0.0)	1/1	(100)	1/1	(100)
Miscellaneous	**6/11**	**(54.5)**	**1/3**	**(33.3)**	**2/4**	**(50.0)**	**3/7**	**(42.9)**
Clostridium difficile toxin, positive	6/10	(60.0)	1/2	(50.0)	2/4	(50.0)	3/6	(50.0)

† 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= Total number of treated patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test postbaseline.
Although a patient may have had two 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.

(Table E-61 modified to include combined comparator data, September 21, 2001 submission)

Medical Officer's Comment: ***With the exception of transaminase increases and serum CPK increase, the incidence of drug-related specific laboratory adverse events occurring in ≥1% of patients were similar. The only study in which serum CPK was obtained was P029 (IM safety study) and although elevated CPK was reported more frequently in the ertapenem group, these elevations were mild and not clinically significant.***

Based on the data regarding laboratory adverse events presented in the preceding table, the Medical Officer recommends that the following drug-related laboratory adverse events occurring in ≥1% of patients receiving ertapenem 1 gm daily be specifically noted in the "Adverse Reactions" section of the label: ALT increased (6.0%), AST increased (5.2%), serum alkaline phosphatase increased (3.4%), eosinophils increased (1.1%), and platelet count increased (2.8%).

The Applicant also assessed the occurence of predefined clinically significant laboratory abnormalities (CSLAs) for specified tests for subjects whose most abnormal laboratory value represented a worsening from baseline. In order to be considered in the population for CSLAs, subjects had to have a baseline laboratory value, at least 1 postbaseline laboratory test, and have normal ranges in the database. For neutrophil counts, the clinical pharmacology studies had a normal range for WBC count and for the percentage of neutrophils. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin, the CSLA criteria were defined in terms of a fixed bound. For total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, and serum creatinine, the CSLA criteria were defined in terms of exceeding a predefined multiple of the ULN. The following table displays the CSLAs for subjects in the Phase II and III studies.

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Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group in All Clinical Studies (Including 14-Day Follow-Up Period)

Number (%) with CSLA

Laboratory Test	CSLA Criteria	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/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%
Absolute Neutrophil Count (cells/*u*L)	<1800	74/1718	4.3	2/51	3.9	5/30	16.7	12/679	1.8	29/846	3.4	41/1525	2.7
	<1000	11/1718	0.6	1/51	2.0	0/30	0.0	1/679	0.1	3/846	0.4	4/1525	0.3
Alanine aminotransferase (U/L)	>2.5 × ULN	97/1606	6.0	5/41	12.2	0/27	0.0	26/618	4.2	47/762	6.2	73/1380	5.3
	>5.0 × ULN	17/1606	1.1	1/41	2.4	0/27	0.0	1/618	0.2	11/762	1.4	12/1380	0.9
Aspartate aminotransferase (U/L)	>2.5 × ULN	101/1727	5.8	5/46	10.9	0/27	0.0	33/679	4.9	35/814	4.3	68/1493	4.6
	>5.0 × ULN	28/1727	1.6	2/46	4.3	0/27	0.0	3/679	0.4	5/814	0.6	8/1493	0.5
Direct serum bilirubin (mg/dL)	>1.5 × ULN	50/974	5.1	2/20	10.0	1/18	5.6	34/414	8.2	13/448	2.9	47/862	5.5
	>2.5 × ULN	29/974	3.0	1/20	5.0	1/18	5.6	20/414	4.8	6/448	1.3	26/862	3.0
Hematocrit (%)	<24	52/1863	2.8	5/62	8.1	0/30	0.0	28/745	3.8	16/908	1.8	44/1653	2.7
Hemoglobin (g/dL)	<8	61/1862	3.3	6/62	9.7	1/30	3.3	30/745	4.0	13/908	1.4	43/1653	2.6
Platelet Count (cells/*u*L)	<75,000	25/1847	1.4	1/62	1.6	1/29	3.4	9/734	1.2	12/904	1.3	21/1638	1.3
	<50,000	14/1847	0.8	1/62	1.6	1/29	3.4	3/734	0.4	4/904	0.4	7/1638	0.4
Serum alkaline phosphatase (U/L)	>2.5 × ULN	49/1699	2.9	3/48	6.3	0/22	0.0	26/668	3.9	13/817	1.6	39/1485	2.6
	>5.0 × ULN	6/1699	0.4	1/48	2.1	0/22	0.0	3/668	0.4	1/817	0.1	4/1485	0.3
Serum creatinine (mg/dL)	>1.5 × ULN	28/1833	1.5	2/59	3.4	1/30	3.3	21/730	2.9	19/894	2.1	40/1624	2.5
	>3.0 × ULN	4/1833	0.2	1/59	1.7	0/30	0.0	4/730	0.5	0/894	0.0	4/1624	0.2
Total serum bilirubin (mg/dL)	>1.5 × ULN	39/1724	2.3	7/46	15.2	1/27	3.7	21/675	3.1	14/823	1.7	35/1498	2.3
	>2.5 × ULN	19/1724	1.1	3/46	6.5	0/27	0.0	9/675	1.3	6/823	0.7	15/1498	1.0

[†] 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 received metronidazole.
N = The total number of treated patients in treatment group.
n/m = Number of patients with CSLA/Number of patients with the laboratory test at baseline and postbaseline.
P/T = Piperacillin/tazobactam.
CTX = Ceftriaxone any dose.
ULN = Upper limit of normal range.

(Table E-64 modified to included combined comparator data, September 21, 2001 submission)

Medical Offer's Comment:: ***The incidence of neutropenia <1800 cells/uL as a CSLA was higher for the ertapenem groups (4.3% in the ertapenem 1 gm group, 3.9% in the ertapenem 1.5 gm group, and 16.7 in the ertapenem 2 gm group) than for the comparator drugs (2.7%). Although the numbers of patients that received ertapenem dosing >1 gm is small, the CSLA results above suggest a possible dose dependent increase in incidence of neutrophil count <1800 cell/uL. When the clinically more significant threshold of neutrophil count <1000 cells/uL is examined the incidence of neutropenia was still greater in the ertapenem groups (0.6% in the ertapenem 1 gm group, 2.0% in the ertapenem 1.5 gm group, and 0% in the***

ertapenem 2 gm group) than for the comparator drugs (0.3%). Of note in 4/11 ertapenem 1 gm patients with ANC <1000 cells/uL (range 234 to 918 cells/uL), the ANC actually increased to >1000 cells/uL (1496 to 15,180 cells/uL) while the patient was still receiving IV ertapenem making toxicity due to ertapenem less likely. The incidence of ANC <1000 cells/uL in the balance of ertapenem 1 gm patients, 7/11 (0.4) was thus similar to that occurring in the combined comparator group, 4/1525 (0.3%).

The incidence of aspartate aminotransferase (AST) elevation >2.5 x ULN and >5 x ULN in patients receiving ertapenem were both greater than in patients receiving comparator drugs combined. The maximal degree of elevation of AST in patients receiving ertapenem 1 gm daily was 25x ULN (on IV therapy), but this patient had an AST of 16x ULN at the prestudy assessment. The remainder of patients had AST elevations of 5x to 13x ULN. Based on the limited number of patients receiving ertapenem 1.5 gm daily there appeared to be an increased incidence of LFT abnormalities associated with the higher ertapenem dose.

The remainder of CSLA findings occurred at similar rates in both the ertapenem 1 gm group and the combined comparator group.

7.2.10 Assessment of Local Tolerability

Phase I Studies

Local tolerability data was collected in 3 Phase I studies in which ertapemen was administered intramuscularly (Protocols 011, 019, and 030). Nine healthy subjects received at least a 1gm IM single dose in Protocol 011. Twenty-one healthy subjects received a 1gm IM dose once daily for 7 days in Protocol 019. Twenty-eight healthy subjects received a 1gm IM dose once daily for days in Protocol 030. The following table displays the number of subjects with local intolerability reactions of moderate-to-severe intensity pooled across these studies.

Number (%) of Subjects With Local Intolerability Symptoms of Moderate-to-Severe Intensity—Intramuscular Injections Only

	Ertapenem (N=58)		Placebo (N=12)	
	n/m	(%)	n/m	(%)
Subjects with one or more symptoms†	5/58	(8.6)	0/12	(0.0)
Pain	4/58	(6.9)	0/12	(0.0)
Swelling	1/58	(1.7)	0/12	(0.0)
Tenderness	1/58	(1.7)	0/12	(0.0)

† Although a subject may have 2 or more symptoms, the subject is counted only once in the overall count.
N = The number of subjects in the treatment group.
n = Number of subjects reporting the tolerability symptom.
m = Number of subjects with an assessment. Subjects with assessments "not done" are not counted.

(Applicant's Table E-13, Volume 2 of 22, page E-55)

Medical Officer's Comment: Of the 5 subjects that received IM ertapenem dosing that are in the preceding table, all had symptoms of moderate intensity. No subject reported symptoms of severe intensity.

Phase II and III Studies

Intravenous

Tolerability at the site of study drug infusion was assessed daily while the patient was on study therapy. Only tolerability data in the Phase IIb and Phase III studies were collected consistently among the studies; therefore, only the Phase IIb and Phase III studies were compared for assessment of tolerability by the Applicant. Of patients who experienced one or more local reactions at the IV infusion site, 389/1743 (22.4%) were in the ertapenem 1 gm group, 200/774 (25.7%) were in the piperacillin/tazobactam group, and 169/750 (22.5%) 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 117/1954 (6.1%) of patients in the ertpenem 1 gm group, 61/774 (7.9%) of patients in the piperacillin/tazobactam group, and 63/942 (6.7%) of patients in the ceftriaxone group. Three patients (0 in the ertapenem 1-g group, 1 in the ceftriaxone group, and 2 in the piperacillin/tazobactam group) were discontinued from study drug therapy due to an adverse experience of infused vein complication in all clinical studies. The following table displays the number (percent) of patients reporting symptoms of local intolerance to IV therapy of any intensity and of moderate to severe intensity in the Phase IIb and Phase III studies.

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Number (%) of Patients With Intravenous Therapy Intolerability Symptoms During Intravenous Therapy Period (Phase IIb and Phase III Studies)

	Ertapenem 1 g (N=1748)†‡		Ertapenem 1.5 g (N=14)		P/T (N=774)†		CTX (N=751)‡	
	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Of Any Intensity (mild, moderate or severe)								
Patients with one or more symptoms‡	**389/1743**	**(22.4)**	**2/14**	**(14.3)**	**199/774**	**(25.7)**	**169/750**	**(22.5)**
Erythema	171/1743	(9.8)	1/14	(7.1)	85/774	(11.0)	77/750	(10.3)
Induration	86/1743	(4.9)	0/14	(0.0)	53/774	(6.8)	24/750	(3.2)
Local phlebitis	83/1743	(4.8)	0/14	(0.0)	44/774	(5.7)	36/750	(4.8)
Other	57/1743	(3.0)	0/14	(0.0)	36/774	(4.7)	11/750	(1.5)
Pain	202/1743	(11.6)	0/14	(0.0)	109/774	(14.1)	71/750	(9.5)
Swelling	106/1743	(6.1)	1/14	(7.1)	74/774	(9.6)	47/750	(6.3)
Tenderness	149/1743	(8.5)	0/14	(0.0)	88/774	(11.4)	57/750	(7.6)
Warmth	80/1743	(4.6)	0/14	(0.0)	40/774	(5.2)	45/750	(6.0)
Of Moderate to Severe Intensity								
Patients with one or more symptoms	**138/1743**	**(7.9)**	**0/14**	**(0.0)**	**66/774**	**(8.5)**	**55/750**	**(7.3)**
Erythema	34/1743	(2.0)	0/14	(0.0)	14/774	(1.6)	14/750	(1.9)
Induration	33/1743	(1.9)	0/14	(0.0)	12/774	(1.7)	12/750	(1.6)
Local phlebitis	32/1743	(1.8)	0/14	(0.0)	15/774	(1.9)	19/750	(2.5)
Other	14/1743	(0.8)	0/14	(0.0)	9/774	(1.2)	4/750	(0.5)
Pain	69/1743	(4.0)	0/14	(0.0)	33/774	(4.1)	22/750	(2.9)
Swelling	29/1743	(1.7)	0/14	(0.0)	20/774	(2.6)	13/750	(1.7)
Tenderness	37/1743	(2.1)	0/14	(0.0)	24/774	(3.1)	18/750	(2.4)
Warmth	21/1743	(1.2)	0/14	(0.0)	9/774	(1.2)	14/750	(1.9)

† 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).
Although a patient may have 2 or more symptoms, the patient is counted only once in the overall count.
P/T = Piperacillin/tazobactam.
CTX = Ceftriaxone.
N = Number of treated patients in the treatment group.
n = Number of patients reporting the intolerability symptom.
m = Number of patients with an assessment. Patients with assessments "not done" were not counted.

(Applicant's Tables E-30 and E-31 [combined], Volume 2 of 22, pages E-195 and E-197)

To address the hypothesis that the proportion of patients in the ertapenem 1 gm group who experienced one or more local reactions at the infusion site would be similar to that observed for patients in the comparator groups, the Applicant determined the observed difference between ertapenem 1 gm group and each comparator group and the 95% CI about the difference. The following table displays the proportion of treated patients who experienced one or more symptoms of local intolerance to IV therapy and the patients with one or more symptoms of moderate to severe intensity.

Number (%) of Patients With Symptoms of Intravenous Therapy Intolerability

Ertapenem 1 g Versus Ceftriaxone

	Treatment Group						Difference (A - B) % (95% CI)
	Ertapenem 1 g (A) (N=942)			Ceftriaxone 1 g (B) (N=750)			
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)	
Patients with one or more symptoms	191/942	(20.3%)	(17.7, 22.8)	169/750	(22.5%)	(19.5, 25.5)	- 2.3 (-6.2, 1.7)
Patients with one or more symptoms of moderate-to-severe intensity	66/942	(7.0%)	(5.4, 8.6)	55/750	(7.3%)	(5.5, 9.2)	-0.33 (-2.8, 2.2)

Ertapenem 1 g Versus Piperacillin/Tazobactam

	Treatment Group						Difference (A - B) % (95% CI)
	Ertapenem 1 g (A) (N=801)			Piperacillin/Tazobactam (B) (N=774)			
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)	
Patients with one or more symptoms	198/801	(24.8%)	(21.8, 27.7)	200/774	(25.8%)	(22.7, 28.9)	-1.06 (-5.3, 3.2)
Patients with one or more symptoms of moderate-to-severe intensity	71/801	(8.9%)	(6.9, 10.8)	67/774	(8.6%)	(6.7,10.6)	0.23 (-2.6, 3.0)

N = Number of treated patients with an assessment.
n/m = Number of patients reporting an intolerability symptom/number of patients with an assessment. Patients with an assessment "not done" were not counted.
CI = Confidence interval.
(Applicant's Tables E-32 and E-33 [combined], September 14, 2001 submission)

Medical Officer's Comment: ***The tolerability of intravenous ertapenem 1 gm was similar to the intravenous tolerability of both the piperacillin/tazobactam group and the ceftriaxone group.***

Intramuscular

An option to convert the route of administration from IV to IM was incorporated into three of the protocols that used ceftriaxone as comparator (Protocols 018, 020, and 021), once pharmacokinetic data on IM administration were available. Both study agents were reconstituted in 1% lidocaine for IM injection. An unblinded nurse or other qualified member of the study staff was designated to prepare and inject the IM doses in order to maintain the blind of the investigator and other study personnel responsible for the assessment of efficacy and safety. Intolerability at the site of IM study drug injection was assessed daily while the patient was on study therapy by the blinded study personnel. Thirty-six total patients received IM therapy: 24 patients in the ertapenem 1 gm group with a mean duration of 3.2 days (range 2 to 10 days) and 12 patients in the ceftriaxone group with a mean duration of 4.3 days (range 2 to 9 days) in Protocols 020 and 021 (no patient received IM therapy in Protocol 018). In addition to the 36 patients that received IM therapy noted above, the Applicant's performed an additional study (Protocol 029) to obtain additional safety and tolerability data for patients receiving IM ertapenem therapy. (The MO's full review of study 029 may be found in Appendix 29.) In study 029, 117 patients received IM therapy: 87 patients in the ertapenem 1 gm group with a mean duration of 4.1 days (range 1 to 7 days) and 30 patients in the ceftriaxone group with a mean duration of 3.8 days (range 1 to 7 days).

For the assessment of tolerability, symptoms were reported separately (e.g., erythema, induration, pain) and graded by intensity (e.g., mild, moderate, severe). The following table

displays the number and percent of patients that received IM study therapy and reported local symptoms of any intensity.

Number (%) of Patients With Local Reaction Symptoms of Any Intensity—During Intramuscular Therapy (Treated Population)

	Ertapenem 1 g (N=111)		Ceftriaxone 1 g (N=42)	
	n/m	%	n/m	%
Patients With One or More Symptoms[1]	31/111	27.9	14/42	33.3
Erythema	1/111	0.9	0/42	0.0
Induration	2/111	1.1	1/42	2.4
Local Phlebitis	0/111	0.0	0/42	0.0
Pain	15/111	13.5	7/42	16.7
Pruritis	0/111	0.0	0/42	0.0
Swelling	0/111	0.0	0/42	0.0
Tenderness	21/111	18.9	5/42	11.9
Ulceration	0/111	0.0	0/42	0.0
Warmth	0/111	0.0	0/42	0.0
Other: ecchymosis	1/111	0.9	0/42	0.0
Other: ecchymosis, injection site	1/111	0.9	2/42	4.8
Other: hematoma, injection site	1/111	0.9	0/42	0.0
Other: rash, papular, injection	1/111	0.9	0/42	0.0
Other: stiffness	0/111	0.0	1/42	2.4

[1] Patients with more than one symptom are counted only once in the overall count.
N = The number of patients in the treatment group.
n = Number of patients reporting the intolerability symptom.
m = Number of patients with an assessment.

(Applicant's Table 40, July 3, 2001 submission, Volume 1 of 1, page 121 modified by results P020 and P021 QTOLER.XPT data sets from original NDA submission)

Medical Officer's Comment: ***Overall ertapenem 1 gm IM daily appeared to be better tolerated than ceftriaxone 1 gm IM daily. The difference in intolerability symptoms of moderate to severe intensity between the two treatment groups is displayed in the following table.***

Number (%) of Patients With Symptoms of Intramuscular Therapy Intolerability (Ertapenem 1-g Versus Ceftriaxone)

	Treatment Group						Difference (A - B)	
	Ertapenem (A) (N=111)			Ceftriaxone 1g (B) (N=42)				
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Patients with one or more symptoms	31/111	27.9%	(19.5, 36.3)	14/42	33.3%	(18.9, 47.8)	-5.4	(-21.9, 11.1)
Patients with 1 or more symptoms of moderate-to-severe intensity	1/111	0.9%	(0.0, 2.7)	4/42	9.5%	(0.5, 18.5)	-8.6	(-17.7, 0.4)

N = Number of treated patients with an assessment.
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

(Table E-34, September 14, 2001 submission)

7.2.11 Safety in Special Populations

7.2.11.1 Geriatric Population

The Applicant reviewed clinical and laboratory adverse experiences during parenteral therapy and the 14-day follow-up periods, in the Phase IIb and Phase III studies, for patients <65 and ≥65 years of age. Of the 3390 treated patients in the Phase IIb and Phase III studies, there were 2482 (1353 in ertapenem 1gm group) patients <65 years of age and 908 (482 in ertapenem 1 gm group) patients ≥65 years of age. According to the Applicant, the overall rate of clinical adverse experiences and the pattern of specific adverse experiences were generally similar for the older and younger populations and the laboratory adverse experience profile was similarly balanced across the groups by age category overall and by specific category of laboratory adverse experiences.

Medical Officer's Comment: ***The overall patterns of clinical adverse experiences and laboratory adverse experiences were generally similar for the older and younger populations; however, as might be expected in an older population with a larger number of co-morbidities and concommitant medications the frequencies were often increased. The increased frequencies of specific adverse events appeared to be balanced across the ertapenem 1 gm and combined comparator groups. Therefore, the MO does not feel any signal was present in the data base to suggest that ertapenem specific drug toxicity was increased in patients ≥65 years old.***

7.2.11.2 Renal Impairment

The Applicant reviewed clinical and laboratory adverse experiences during the parenteral therapy period and the entire study period, including specific as well as serious adverse experiences, for patients in all Phase IIb and Phase III studies by the absence or presence of renal dysfunction, defined as creatinine clearance ≥60 mL/min/1.73 m2 (either as provided by investigator, or if not provided, then calculated from data provided using the calculation of Cockcroft and Gault[12]) or if creatinine clearance could not be calculated, by pretreatment serum creatinine of >2 mg/dL. The numbers of patients with renal dysfunction, as defined above, were 382 in the ertapenem 1gm group, 87 patients in the piperacillin/tazobactam group, and 220 patients in the ceftriaxone group. The proportion of patients with one or more clinical adverse experiences, during the parenteral therapy plus 14-day follow-up periods, in the normal renal function group were 816/1451 (56.2%) for ertapenem 1 gm, 414/687 (60.3%) for piperacillin/tazobactam, and 328/560 (58.6%) for ceftriaxone. For patients with renal dysfunction, these rates were 236/382 (61.8%) for ertapenem, 64/87 (73.6)% for piperacillin/tazobactam, and 131/220 (59.5%) for ceftriaxone. The Applicant also examined the laboratory adverse experience profile by the absence or presence of renal dysfunction in patients who had laboratory adverse experiences. According to the Applicant the proportion of patients with one or more clinical or laboratory adverse experiences for patients in the absence or presence of renal dysfunction were generally similar in the 3 treatment groups.

Medical Officer's Comment: ***The overall patterns of clinical adverse experiences and laboratory adverse experiences were generally similar for patients with normal renal function (≥60 mL/min/1.73 m^2) and patients with decreased renal***

[12] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976(16):31-41.

function (<60 mL/min/1.73 m^2); however, as might be expected in a population with impaired renal function with a larger number of co-morbidities and concommitant medications the frequencies were often increased. The increased frequencies of specific adverse events appeared to be balanced across the ertapenem 1 gm and combined comparator groups. Therefore, the MO does not feel any clear signal was present in the database to suggest that ertapenem specific drug toxicity was increased in patients with creatinine clearance <60 mL/min/1.73 m^2.

Of note, the rate of seizure disorder in the ertapenem 1 gm group did increase from 4/1451 (0.3%) in patients with normal renal function to 4/382 (1.0%) in patients with renal dysfunction, as defined by the Applicant. The MO thus recommends that specific cautions regarding the potential for seizures in patients with renal dysfunction be included in the label as it is for the currently marketed carbapenems.[13,14]

7.2.11.3 Hepatic Impairment

The Applicant has not conducted any Phase I studies in subjects with hepatic impairment; however, based on Phase I study data provided, it is expected that hepatic clearance accounts for <10% of the total clearance of ertapenem.

The Applicant did not provide any analyses that address the incidence of adverse events in patients with hepatic impairment who enrolled in clinical studies.

***Medical Officer's Comment:** As was discussed in FDA review team meetings, the lack of specific studies in subjects or patients with hepatic impairment will make it impossible to provide specific dosing guidelines for patients with hepatic impairment in the product label. To bolster the information available to determine the most appropriate dosing recommendations for patients with hepatic impairment, the Applicant has been asked to review their clinical study databases to identify patients with pre-existing hepatic impairment that were enrolled in Phase II and III studies and to provide analyses of adverse events for this subpopulation of patients.*

7.2.11.4 Safety by Race

The Applicant reviewed clinical and laboratory adverse experiences during parenteral therapy plus the 14-day follow-up period for patients in the Phase IIb and Phase III studies by race. Of the 3390 treated patients in the Phase IIb and Phase III studies, there were 427 Black (12.6%), 1822 Caucasian (53.7%), 813 Hispanic (24.0%), and 328 "Other" race (9.8%) patients. The Applicant noted that there appeared to be differences in the overall rates of laboratory adverse experiences specifically in the rates of AST and ALT elevations by race across all treatment groups, with reporting rates highest for Hispanic, lowest for Blacks, and between the 2 extremes for Caucasians.

***Medical Officer's Comment:** To further examine the apparent increased rate of LFT adverse events reported for "Hispanics," the MO reviewed the more clinically significant group of "clinically significant laboratory abnormalities" for AST >5x ULN by race. When the data were reviewed in this manner, the frequency of AST >5x ULN was more similar across all racial groups, but was still higher in the "Hispanic" category for both ertapenem and ceftriaxone. The MO performed a PubMed search to determine if similar occurrences have been reported for other drugs, but found no listings to suggest hepatic drug toxicity of any type was more common in Hispanic patients.*

In addition to the apparent differences in rates of LFT abnormalities noted by the Applicant, the MO also observed that neutropenia and decreased WBC counts occurred at a higher frequency in the racial group designated as "Other" ("Other" included Latin American, Asian, Philippina, Indian, Spanish, Polynesian, Mexican, Mulatto, Spanish American, Colored, Armenian, Maori, Mixed, Hispanic/White, African, and not specified.) by the Applicant. Since "laboratory adverse events" were reported at the discretion of the Investigator without regard to the degree of neutropenia or decreased WBC, the MO reviewed the more clinically significant group of "clinically significant laboratory

[13] PRIMAXIN® IV (Imipenem and Cilastatin for Injection) Current Product Labeling
[14] MERREM® IV (Meropenem for Injection) Current Product Labeling

abnormalities" for absolute neutrophil count (ANC) <1000 cells/uL by race. When the data were viewed in this manner, the frequency of ANC <1000 cells/uL was more similar across all racial groups, although still slightly greater in the "other" category.

The discrepancies among racial groups are displayed in the following table.

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Number (%) of Patients With Specific Laboratory Adverse Events- By Race During Study Therapy and 14-Day Follow-Up Period for Phase IIb and Phase III Studies

	Black						Caucasian						Hispanic						Other					
	Ertapenem N=240		P/T N=109		CTX N=78		Ertapenem 1 gm N=968		P/T N=366		CTX N=488		Ertapenem 1 gm N=453		P/T N=217		CTX N=143		Ertapenem 1 gm N=174		P/T N=82		CTX N=72	
	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%
Patients with one or more AEs	34/222	15.3	17/103	16.5	21/77	27.3	234/934	25.1	118/359	32.9	88/474	18.6	162/442	36.7	64/213	30.0	47/139	33.8	73/173	42.2	35/80	43.8	32/71	45.1
Patients with no AEs	188/222	84.7	86/103	83.5	56/77	72.7	700/934	74.9	241/359	67.1	386/474	81.4	280/442	63.3	149/213	70.0	92/189	66.2	100/173	57.8	45/80	56.3	39/71	54.9
ALT increased	8/185	4.3	3/87	3.4	2/61	3.3	63/857	7.4	25/322	7.8	26/436	6.0	53/417	12.7	19/197	9.6	17/131	13.0	14/171	8.2	3/79	3.8	7/70	10.0
AST increased	8/205	3.9	5/96	5.2	2/70	2.9	58/905	6.4	30/348	8.6	24/448	5.4	52/423	12.3	20/202	9.9	15/136	11.0	11/168	6.5	5/80	6.3	11/70	15.7
CSLA AST > 5x ULN	2/205	1.0	1/96	1.0	0/70	0.0	12/905	1.3	1/348	0.3	1/448	0.2	12/423	2.8	1/202	0.4	3/136	2.2	2/168	1.2	0/80	0.0	1/70	1.4
Serum alkaline phosphatase increased	4/203	2.0	1/97	1.0	1/72	1.4	35/908	3.9	28/351	8.0	10/451	2.2	39/414	9.4	21/194	10.8	4/136	2.9	9/172	5.2	2/80	2.5	4/71	5.6
Segmented neutrophils decreased	1/213	0.5	0/94	0.0	0/72	0.0	4/915	0.4	1/349	0.3	0/461	0.0	7/418	1.7	0/195	0.0	2/138	1.4	9/172	5.2	1/79	1.3	3/71	4.2
WBC count decreased/WBC decreased	1/219	0.5	0/99	0.0	4/77	5.2	7/930	0.8	2/358	0.6	3/467	0.6	5/439	1.1	2/211	0.9	2/138	0.7	9/171	5.3	1/80	1.3	3/71	4.2
CSLA of Absolute Neutrophil Count < 1000 cells/uL	1/219	0.5	1/99	1.0	1/77	1.3	4/930	0.4	0/358	0.0	1/467	0.2	3/439	0.6	0/211	0.0	0/138	0.0	3/171	1.8	0/80	0.0	1/71	1.4

Ertapenem=1 gm group
P/T=piperacillin/tazobactam
CTX=ceftriaxone 1 gm group
N=Total number of patients per treatment group.
n/m=Number of patients with laboratory adverse event/number of patients with laboratory test.

7.2.11.5 Safety by Gender

The Applicant reviewed clinical and laboratory adverse experiences during parenteral therapy plus the 14-day follow-up periods, in the Phase IIb and Phase III studies, by gender. Of the 3287 treated patients in the Phase IIb and Phase III studies, there were 1548 men (47.1%) and 1739 (52.9%) women. According to the Applicant, the proportion of patients treated with ertapenem 1 gm with one or more clinical or laboratory adverse experiences reported and the pattern of specific adverse experiences were similar in both genders.

Medical Officer's Comment: *As is displayed in the table below, nausea and vomiting appeared to be more frequent in females than males. Although the difference was most pronounced in the ertapenem group, it was also seen to a lesser degree in the comparator groups. Whether this represents a differential toxicity profile or a difference in reporting habits between males and females cannot be determined.*

The laboratory adverse events of increased ALT and AST were more common in males across all treatment groups.

	Male Patients						Female Patients					
	Ertapenem N=841		P/T N=368		CTX N=365		Ertapenem 1 gm N=968		P/T N=366		CTX N=488	
	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%
Patients with one or more AEs	464/841	55.2	233/368	63.3	204/365	55.9	590/994	59.4	245/406	60.3	255/416	61.3
Patients with no AEs	377/841	44.8	135/368	36.7	161/365	44.1	404/994	40.6	161/406	39.7	161/416	38.7
Nausea	40/841	4.8	28/368	7.6	18/365	4.9	87/994	8.8	39/406	9.6	31/416	7.5
Vomiting	17/841	2.0	16/368	4.3	9/365	2.5	50/994	5.0	25/406	6.2	10/416	2.4
ALT increased	84/747	11.2	32/329	9.7	28/334	8.4	54/883	6.1	18/356	5.1	24/364	6.6
AST increased	78/780	10.0	41/350	11.7	26/341	7.6	51/921	5.5	19/376	5.1	26/383	6.8

Ertapenem=1 gm group
P/T=piperacillin/tazobactam
CTX=ceftriaxone 1 gm group
N=Total number of patients per treatment group.
n/m=Number of patients with laboratory adverse event/number of patients with laboratory test.

7.2.11.6 Human Pregnancy Outcome Data

One patient (AN 4986) in Protocol 016, in the MK-0826 group, was pregnant at study entry. This pregnancy was discovered on Study Day 6. The patient experienced a spontaneous abortion on Study Day 6 and was discontinued from study drug therapy. In the opinion of the investigator, this adverse experience was serious and considered probably related to the study drug therapy. The Applicant's narrative description of this case follows:

AN 4986

A 22-year-old female began IV MK-0826 therapy for the treatment of a perineal abscess. A blood sample was taken at the time of study entry, but results of the serum b-HCG assay were not available to the investigator until Study Day 6. On this day, the results of the serum pregnancy test were found to be positive, but the patient began to experience genital bleeding related to an incomplete spontaneous abortion. On Study Day 7, a pelvic transabdominal sonogram was performed and the results were consistent with the fourth week of pregnancy. Study

drug therapy was discontinued on Study Day 7 and a uterine curettage was performed. In the opinion of the investigator, the spontaneous abortion was probably related to the study drug therapy.

Medical Officer's Comment: ***Given that this is the only experience in a pregnant woman that is available for ertapenem, the MO recommends that a comment regarding the outcome in this patient be included in the "Pregnancy Category" section of the label.***

7.2.12 Review of Systems

Adverse events occurring in the Phase II and III clinical studies, by specific body system, will be reviewed in this section and, when appropriate, results from Phase I clinical and pre-clinical studies will be mentioned. Labeling for currently marketed carbapenems (imipenem and meropenem) will be provided to present historical incidence rates for adverse events previously reported for this class of antimicrobials. In addition, the recommendations for those adverse events that the Medical Officer believes should be included in the Invanz label will be presented. To determine which adverse events will be included, the Medical Officer will apply the following set of criteria:

1. Selection of adverse events for inclusion will be based on the overall incidence of the adverse event, not the drug-related adverse event incidence.
2. Selection of adverse events for inclusion will be based on the reporting period of study therapy plus 14 day follow-up period, not on the parenteral therapy only period.
3. Adverse events occurring in 3 or more patients (>0.1%) in the ertapenem 1 gm group will be included unless they were clearly related to treatment failure or would be considered to have no clinical significance.
4. Adverse events occurring in 2 or fewer patients (≤0.1%) in the ertapenem 1 gm group will only be included if they have been previously associated with the carbapenem class of antimicrobials, if they would be predicted to occur based on pre-clinical data, or if they are likely to result in potentially serious adverse events.

7.2.12.1 Body as a Whole

For currently marketed carbapenems the following adverse clinical events have been noted:

Primaxin I.V. -In the "Adverse Reactions" section of the label, fever (0.5%) was reported as possibly, probably, or definitely related to imipenem.

Merrem I. V. - In the "Adverse Reactions" section of the label, adverse events related to "Body as a Whole" that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: pain, abdominal pain, chest pain, sepsis, shock, fever, abdominal enlargement, back pain, and hepatic failure.

The following table displays adverse events related to "Body as a whole" that occurred in ≥0.1% of patients receiving ertapenem 1 gm daily during the parenteral period plus 14-day follow-up period.

Medical Officer's Comment: ***The clinical drug-related and non-drug-related adverse events related to "Body as a whole" occurred at similar rates (see prior death discussion) between the ertapenem 1 gm group and the combined comparator group.***

Based on the Medical Officer's criteria for inclusion of adverse events in the "Adverse Reactions" section of the label the Medical Officer recommends that the following adverse events be included under "Body as a Whole": asthenia/fatigue (1.2%), candidiasis (0.3%), chills (0.5%), death (1.8%), dehydration (0.4%), abdominal distention (0.8%), edema/swelling (3.1%), facial edema (0.2%), fever (3.4%), gout (0.4%), injection site induration (0.2%), malaise (0.4%), necrosis (0.4%), pain (0.6%), injection site pain (0.2%), abdominal pain (4.0%), chest pain (1.2%), flank pain (0.2%), septicemia (0.5%), septic shock (0.5%), syncope (0.2%), and weight loss (0.3%).

Number (%) of Patients With Body as a Whole Clinical Adverse Experiences (Incidence ≥0.1 % in Ertapenem 1 gm Group) During Study Therapy and 14-Day Follow-Up Period—All Clinical Studies (Total and Drug Related)

	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
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**
Adenocarcinoma	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Amebiasis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Asthenia/fatigue	24	(1.2)	3	0	(0.0)	0	0	(0.0)	0	7	(0.9)	1	10	(1.1)	1
Bacteremia	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Candidiasis	6	(0.3)	4	0	(0.0)	0	0	(0.0)	0	4	(0.5)	3	3	(0.3)	2
Cardiopulmonary failure	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Chills	10	(0.5)	1	0	(0.0)	0	0	(0.0)	0	7	(0.9)	1	4	(0.4)	0
Cold sensation	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Death	35	(1.8)	0	3	(4.7)	0	0	(0.0)	0	12	(1.6)	0	15	(1.6)	0
Deterioration, general	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	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
Drainage, wound	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Drug overdose	8	(0.4)	2	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Ecchymosis, injection site	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Edema/swelling	60	(3.1)	3	3	(4.7)	0	0	(0.0)	0	19	(2.5)	2	31	(3.3)	2
Edema, facial	3	(0.2)	1	0	(0.0)	0	0	(0.0)	0	2	(0.3)	2	3	(0.3)	0
Fever	66	(3.4)	3	7	(10.9)	0	0	(0.0)	0	51	(6.6)	1	32	(3.4)	2
Fistula	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Flu-like illness	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hernia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hernia, abdominal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hernia, diaphragmatic	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hyperthermia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Induration, injection site	3	(0.2)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	1
Infection	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Infection, CMV	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, fungal	10	(0.5)	5	0	(0.0)	0	0	(0.0)	0	5	(0.6)	5	10	(1.1)	7
Infection, herpes	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infestation, parasitic	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Inflammation	3	(0.2)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Malaise	8	(0.4)	3	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	3	(0.3)	0
Mass	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Multiple organ failure	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Necrosis	8	(0.4)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	0	(0.0)	0
Neoplasm, malignant	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Pain	11	(0.6)	3	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	12	(1.3)	4
Pain/tenderness/soreness, injection site	4	(0.2)	3	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	3	(0.3)	1
Pain, abdominal	78	(4.0)	17	4	(6.3)	0	1	(3.3)	0	37	(4.8)	4	37	(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, flank	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	6	(0.6)	0

7.2.12.2 Cardiovascular

Phase I Studies

Limited data are available from Phase I trials regarding the effect of ertapenem on ECG parameters. Based on data from the 10 Phase I studies, reported in the NDA, in which ECGs were performed, the Applicant has stated that ertapenem does not have any significant effect on the QT interval.

Medical Officer's Comment: ***The following table displays available data relating to the issue of potential for QT prolongation available that have been submitted to the NDA.***

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Summary QT/ QTc Data from Ertapenem Clinical Pharmacology Studies

Protocol	Study Description	Ertapenem† Subjects (N=220)	Placebo Subjects (N=32)	Duration of Drug Admin (Days)	Method of QTc Measurement	Number of Subjects QTc>450msec		Number of Subjects ΔQTc>30 msec	
						Ertapenem	Placebo	Ertapenem	Placebo
001	Single/multiple rising rose	50	16	1 to 15	By Merck using machine calculated QT and Bazett's correction*	1	1	3	2
009	Dose proportionality	16	0	4	Machine calculated using Bazett's correction*	0	0	2	0
010	Pharmacokinetics in elderly	15	0	1 and 7	Machine calculated using Bazett's correction*	1	0	1	0
011	Pilot intramuscular administration	9	2	2	Machine calculated using Bazett's correction*	0	0	1	0
012	Radiolabelled disposition	7	0	1	Machine calculated using Bazett's correction*	0	0	0	0
013	14-day intravenous safety	20	4	14	Machine calculated using Bazett's correction*	0	0	3	0
019	Intramuscular/intravenous administration comparison	22	4	10	Machine calculated using Bazett's correction*	1	0	2	0
027	Effect of probenecid	14	0	2	Machine calculated using the formula: [redacted]	0	0	2	0
030	Multiple-dose intramuscular safety	28	6	3	Machine calculated using Bazett's correction*	0	0	0	0

† Ertapenem includes subjects who received ertapenem alone (N=206) and with probenecid (N=14).
* QTc=QT divided by the square root of the RR interval. The RR interval was calculated as 60 divided by the ventricular rate (in seconds)
(Derived by Medical Officer from data set provided by Applicant in August 30, 2001 submission)

In interpreting the QT interval data provided by the Applicant, it should be kept in mind that all of the Applicant's QT and QTc data are derived from the readings printed on ECGs and transcribed to CRF reports without being overread by a qualified individual.

The QTc was increased, on at least one occasion, by greater than 30 msec (range 30-65 msec) in 14/220 (6.7%) subjects that received ertapenem and 2/32 (6.3%) subjects that received placebo. Four subjects had a QTc >450msec (all calculated using Bazett's calculation). One of the four was receiving placebo (1/32 [3.1%]) and three were receiving ertapenem (3/220 [1.4%]). One female ertapenem subject (in P001) had a QTc of 413 msec prestudy and a QTc of 453 msec 8 hours after receiving a dose of 250 mg. This subjects QTc was <450 msec at 24 hours after the 250mg dose, on 8 and 24 hour ECGs after 1000mg dose, and on 8 and 24 hour ECGs after the 2000mg dose. One male ertapenem subject in protocol 010 had a QTc of 452 msec after the second dose of ertapenem, but this value was a decrease from the subjects pre-study value of 469 msec. One additional female ertapenem subject on protocol 019 had a baseline QTc of 438 msec and a QTc of 462 msec after receiving a 1 gm IM dose. Overall it appears that QTc increases of >30 msec and absolute QTc values >450 msec were similar in the treatment and placebo groups, suggesting that there is no effect of ertapenem on the QTc interval at the time points measured. The Applicant has performed an additional Phase I study (Protocol 035) to assess the potential for increases of QTc immediately post 30 minute infusion and 1 hour post 30 minute infusion of ertapenem 2 gms IV. The Applicant has stated that no evidence of QT prolongation was seen in this study, but, the study report has not been submitted to the NDA for review.

To further explore the potential for ertapenem to cause increased QTc, the FDA review team requested that OPDRA investigate the incidence of adverse events reported in the Medwatch system for the currently marketed carbapenems. Dr. Ronald Wassell, OPDRA, performed the requested review. In his review he compared the incidence of QTc related adverse events (in the AERS database) associated with the use of the currently marketed carbapenem class drugs (imipenem and meropenem) to the beta-lactam controls (ceftriaxone and piperacillin/tazobactam). Dr. Wassell concluded that "given the length of time these products have been on the market and the amount of usage they have received, the lack of quality reports would appear to indicate that there is no signal for QTc related adverse events associated with the use of the currently marketed carbapenem class drugs (imipenem and meropenem)."

Given that QT prolongation is not a known toxicity for B-lactam antimicrobials in general and did not appear to be an issue for the currently marketed carbapenems in particular, the Medical Officer does not feel that specific labeling regarding QT prolongation is warranted in the label. The Applicant, however, should be required to submit the final study report for Protocol 035 as a Phase IV commitment.

Phase II/III Studies

For currently marketed carbapenems the following cardiovascular adverse clinical events have been noted:

Primaxin I.V. - Possibly, probably or definitely drug related cardiovascular adverse events that occurred in less than 0.2% of patients or that were reported since the drug has been marketed included palpitations and tachycardia. In addition, adverse local reactions that were reported as possibly, probably, or definitely related to therapy were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), and infused vein complication (0.1%).

Merrem I. V. - Systemic cardiovascular adverse clinical events that were reported in less than 1.0% but greater than 0.1% of patients, irrespective of the relationship to meropenem, included: heart failure, heart arrest, tachycardia, hypertentsion, myocardial infarction, pulmonary embolus, bradycardia, hypotension, and syncope. In addition, adverse local reactions that were reported irrespective of the relationship to therapy

were: inflammation at the injection site (2.4%), phlebitis/thrombophlebitis (0.8%), injection site reaction (0.9%), pain at the injection site (0.4%), and edema at the injection site (0.2%).

The following table displays the systemic and local cardiovascular adverse events that occurred in ≥0.1% of patients receiving ertapenem 1 gm daily during the parenteral period plus the14-day follow-up period.

Medical Officer's Comment: ***Notably, there were a total of 11 adverse events of cardiac arrest (10 [0.5%] in the ertapenem 1 gm group and 1 [0.1%] in the combined comparator groups) during the parenteral period plus 14 day follow-up period. None of these events was considered study drug related by the investigators. Of the 10 episodes that occurred in the ertapenem 1 gm group, 9 patients (5 enrolled in P017, 2 enrolled in P018, and 1 enrolled in P023) were also reported to experience subsequent death. Based on the MO's review of CRFs, narratives, and additional requested information, the MO believes that the events surrounding cardiac arrest and death in 3/9 of these patients were related to treatment/surgical failure, 1/9 due to pulmonary embolism, 1/9 due to congestive heart failure, 1/9 due to underlying diseases, 1/9 was remote (18 days) from the last day of study drug making drug toxicity unlikely, and 2/9 were due to unexplained causes. Based on the MO's review of the one episode of cardiac arrest that occurred in the comparator groups, the MO believes that the events surrounding the cardiac arrest and death in this patient were due to unexplained causes. Thus, the events of unexplained cardiac arrest were similar between the ertapenem 1 gm group and the comparator groups.***

Based on the Medical Officer's criteria for inclusion of adverse events in the "Adverse Reactions" section of the label the Medical Officer recommends that the following adverse events be included under "Cardiovascular": arrhythmia (0.3%), asystole (0.2%), atrial fibrillation (0.3%), bradycardia (0.4%), cardiac arrest (0.5%), CVA (0.2%), extravasation (1.2%), heart failure (0.6%), hematoma (0.5%), subdural hemorrhage (0.2%), hypertension (1.1%), hypotension (1.4%), infused vein complication (6.1%), heart murmur (0.3%), phlebitis/thrombophlebitis (1.7%), tachycardia (1.4%), and ventricular tachycardia (0.3%).

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Number (%) of Patients With Cardiovascular System Clinical Adverse Experiences (Incidence ≥0.1 % in Ertapenem 1 gm Group) During Study Therapy and 14-Day Follow-Up Period—All Clinical Studies (Total and Drug Related)

	Ertapenem 1 g (N=1954)[1,2]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[1]			Ceftriaxone (N=942)[1,5]		
	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR	n	(%)	DR
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
Atrial fibrillation	5	(0.3)	0	3	(4.7)	0	0	(0.0)	0	6	(0.8)	0	4	(0.4)	1
Atrial flutter	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Atrial tachycardia	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
AV block, first degree	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
AV block, third degree	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Bleeding, postoperative	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Blood pressure decreased	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
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
Cardiac arrest	10	(0.5)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cardiac tamponade	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cardiovascular disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cerebrovascular disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Cold extremities	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Compression, vein	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cor pulmonale	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	5	(0.5)	0
CVA	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
ECG abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Embolism/infarction, pulmonary	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Endocarditis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	13	(1.7)	6	10	(1.1)	4
Extravasation	23	(1.2)	8	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Gangrene	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Heart disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	8	(0.8)	0
Heart failure	12	(0.6)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	0	(0.0)	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	0	(0.0)	0	5	(0.5)	3
Hemorrhage, IV site	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemorrhage, subdural	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	11	(1.4)	1	9	(1.0)	1
Hypertension	21	(1.1)	0	2	(3.1)	0	0	(0.0)	0	6	(0.8)	0	2	(0.2)	0
Hypertension increased	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypertension, borderline	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypertension, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Hypertensive crisis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	11	(1.4)	1	11	(1.2)	1
Hypotension	28	(1.4)	3	3	(4.7)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Infection, infused vein	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	61	(7.9)	43	63	(6.7)	43
Infused vein complication	119	(6.1)	73	2	(3.1)	2	3	(10.0)	1	0	(0.0)	0	1	(0.1)	0
Murmur, heart	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	3	(0.3)	0
Myocardial infarction	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0						

Occlusion, arterial, lower extremity	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Occlusion, iliac artery	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pain, catheter, cardiac	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Pericardial rub	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pericarditis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	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
Phlebolith	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Premature ventricular contraction	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Shock	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Sinus arrhythmia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Sinus tachycardia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Supraventricular premature beat	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Supraventricular tachycardia	4	(0.2)	1	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0
Syncope	28	(1.4)	1	1	(1.6)	0	1	(3.3)	0	10	(1.3)	0	3	(0.3)	0
Tachycardia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	7	(0.7)	0
Thrombosis	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	1	1	(0.1)	0
Thrombosis, deep vein	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Transient ischemic attack	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Valvular disorder	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Vasculitis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Venous insufficiency	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Venous pressure decreased	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0
Ventricular tachycardia															

(Modified from Applicant's Reference 46, September 21, 2001 submission)

7.2.12.3 Nervous/Psychiatric

For currently marketed carbapenems, the following adverse clinical events have been noted:

Primaxin I.V. -In the "Adverse Reactions" section of the label, seizures (0.4%) and somnolence (0.2%) were reported as possibly, probably, or definitely related to imipenem. Additional adverse events related to the nervous system that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, and psychic disturbances including hallucinations. (Specific cautions regarding seizures and other CNS events are also contained in the "Warnings" and "Precautions" sections of the label.)

Merrem I. V. - In the "Adverse Reactions" section of the label, headache was reported in 2.8% of patients irrespective of the relationship to meropenem. Additional adverse events related to the nervous system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: insomnia, agitation/delerium, confusion, dizziness, seizure, nervousness, paresthesia, hallucinations, somnolence, anxiety, and depression. (Specific cautions regarding seizures and other CNS events are also contained in the "Warnings" and "Precautions" sections of the label.)

The following table displays adverse events related to the nervous system that occurred in ≥0.1% of patients receiving ertapenem 1 gm daily during the parenteral period plus 14-day follow-up period.

Medical Officer's Comment: ***Seizure disorder, seizure (focal), and seizure (grand mal) have been reported separately by the Applicant in their analyses of adverse events. The MO believes that combining these three categories into an "overall seizure" category may provide a better estimate of seizure related adverse events. When this was done an adverse event of "overall seizure" occurred in 10/1954 (0.5%) of patients receiving ertapenem 1 gm and 2/1716 (0.1%) of patients receiving comparator drugs. The drug-related adverse event of "overall seizure was 3/1954 (0.2%) of patients receiving ertapenem 1 gm and 1/1716 (0.1%) of patients receiving comparator drugs. Of the patients that had an adverse event of seizure, (4/10 receiving ertapenem and 1/2 receiving piperacillin/tazobactam) had a pre-existing history of a seizure disorder. Based on the MO's review of CRFs and narratives for these patients, the MO believes that seizures were unlikely to be related to parenteral study drugs in 5/10 ertapenem patients due to the timing of seizures (ANs 6413 and 6417) or underlying concommitant illnesses (ANs 4376, 4695, and 7478). However, given the seriousness of this adverse event and the known association of carbapenems with the adverse event of seizure, the MO recommends that specific labeling regarding seizure potential be included in the "Warnings" and "Precautions" sections of the label, in addition to the "Adverse Reactions" section of the label.***

Multiple listings that are consistent with an alteration in mental status (agitation, confusion, disorientation, mental acuity decreased, mental status change, somnulence, and stupor) have also been reported by the Applicant separately. The MO believes that combining these events categories into an "overall altered mental status" category may provide a better estimate of adverse events reflecting changes to mental status. When this was done an adverse event of "overall altered mental status" occurred in 78/1954 (4.0%) of patients receiving ertapenem 1 gm and 50/1716 (2.9%) of patients receiving comparator drugs. The drug-related adverse event of "overall altered mental status" was 15/1954 (0.8%) of patients receiving ertapenem 1 gm and 11/1716 (0.6%) of patients receiving comparator drugs.

The remainder of clinical drug-related and non-drug-related adverse events related to the nervous system occurred at similar rates between the ertapenem 1 gm group and combined comparator group.

Based on the Medical Officer's criteria for inclusion of adverse events in the "Adverse Reactions" section of the label the Medical Officer recommends that the following adverse events be included under "Nervous System & Psychiatric": aggressive behavior (0.2%), alteration in mental status (combined grouping of agitation, confusion, disorientation, hallucinations, mental acuity decreased, mental status change, psychic disturbance, somnolence, and stupor) (%), depression (0.3%), dizziness (1.7%), headache (6.3%), hypesthesia (0.3%), insomnia (3.1%), nervousness (0.5%), paresthesia (0.2%), seizure (combined grouping of seizure disorder, focal seizure, and grand mal seizure) (0.5%), spasm (0.3%), tremor (0.4%), and vertigo (0.1%).

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Number (%) of Patients With Nervous System Clinical Adverse Experiences (Incidence ≥1 % in Ertapenem 1 gm Group) During Study Therapy and 14-Day Follow-Up Period—All Clinical Studies (Total and Drug Related)

	Ertapenem 1 g (N=1954)[‡‡]			Ertapenem 1.5 g (N=64)			Ertapenem 2 g (N=30)			Piperacillin/Tazobactam (N=774)[†]			Ceftriaxone (N=942)[‡§]		
Nervous System and Psychiatric Disorder	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**
	323	**(16.5)**	**79**	**17**	**(26.6)**	**2**	**6**	**(20.0)**	**3**	**140**	**(18.1)**	**23**	**157**	**(16.7)**	**40**
Aggressive behavior	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Agitation	18	(0.9)	2	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	3	(0.3)	0
Alcohol withdrawal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Anxiety	20	(1.0)	1	0	(0.0)	0	0	(0.0)	0	10	(1.3)	1	11	(1.2)	0
Anxiety disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Confusion	39	(2.0)	4	5	(7.8)	1	0	(0.0)	0	14	(1.8)	2	8	(0.8)	0
Crying	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Delirium	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dementia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Depression	6	(0.3)	1	1	(1.6)	0	0	(0.0)	0	8	(1.0)	1	2	(0.2)	0
Depressive disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Disorientation	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Dizziness	34	(1.7)	14	1	(1.6)	0	0	(0.0)	0	23	(3.0)	5	20	(2.1)	7
Dream abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Drug abuse	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Drug withdrawal disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dysphasia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dystonia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Falling	7	(0.4)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Gait abnormality	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
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
Hypersomnia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypertonia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypesthesia	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	1	2	(0.2)	0
Insomnia	61	(3.1)	6	3	(4.7)	0	0	(0.0)	0	40	(5.2)	1	39	(4.1)	1
Mental acuity decreased	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
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
Neuropathy, peripheral	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Paresthesia	3	(0.2)	2	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	2
Psychic disturbance	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Psychogenic musculoskeletal disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Restless leg syndrome	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Seizure disorder	8	(0.4)	2	0	(0.0)	0	0	(0.0)	0	2	(0.3)	1	0	(0.0)	0
Seizure, focal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Seizure, grand mal	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Sleep disorder	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	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
Spasm	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Stupor	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Tremor	7	(0.4)	2	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0
Vertigo	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0

(From Applicant's Reference 46, September 21, 2001 submission)