7.2.12.4 Gastrointestinal

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

Primaxin I.V. -In the "Adverse Reactions" section of the label, nausea (2.0%), diarrhea (1.8%), and vomiting (1.5%) were reported as possibly, probably, or definitely related to imipenem. Additional adverse events related to the gastrointestinal system that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: pseudomembranous colitis, hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillary hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, and increased salivation. Laboratory changes related to the gastrointestinal system that were reported in the label without regard to drug relationship included: increased ALT, AST, alkaline phosphatase, bilirubin, and LDH.

Merrem I. V. - In the "Adverse Reactions" section of the label, the incidence of diarrhea (5.0%) and nausea/vomiting (3.9%) were reported irrespective of the relationship to meropenem. Additional adverse events related to the gastrointestinal system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, and ileus. Laboratory changes related to the gastrointestinal system that were reported in the label without regard to drug relationship included: increased ALT, AST, alkaline phosphatase, LDH, and bilirubin.

The following table displays adverse events related to the gastrointestinal 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: ***The clinical drug-related and non-drug-related adverse events related to the gastrointestinal system occurred at similar rates between the ertapenem 1 gm group and combined comparator group. The incidences of diarrhea, constipation, nausea, and vomiting for the ertapenem 1 gm appear to be greater than those historical rates reported in the imipenem and meropenem labels, but the rates of diarrhea, constipation, nausea, and vomiting reported for the comparator agents in this NDA were also greater than those historical rates reported in their respective labels.***

An ertapenem dose-related incidence of diarrhea, nausea, and vomiting was not as strongly suggested by data in the Phase II and III clinical studies as it had been by data in the Phase I clinical studies.

Clinically significant laboratory adverse events related to the gastrointestinal system occurred at similar rates between the ertapenem 1 gm group and combined comparator group, with the exception of AST increases as was noted in section 7.2.9 of this review.

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 "Digestive System": acid regurgitation (1.3%), anorexia (0.5%), oral candidiasis (0.9%), cholelithiasis (0.2%), constipation (3.6%), diarrhea (9.7%), Clostridium difficile associated diarrhea (0.4%), duodenitis (0.2%), dyspepsia (1.1%), dysphagia (0.3%), esophagitis (0.2%), flatulence (0.5%), gastritis (0.2%), gastrointestinal hemorrhage (combined adverse experiences of hematemesis, hematochezia, anal/rectal hemorrhage, gastrointestinal hemorrhage, and melena) (0.7%), hemorrhoids (0.3%), ileus (0.3%), jaundice (0.2%), nausea (7.3%), pancreatitis (0.1%), pyloric stenosis (0.1%), stomatitis (0.4%), mouth ulcer (0.2%), and vomiting (3.9%).

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Number (%) of Patients With Gastrointestinal System Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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
Digestive System	**500**	**(25.6)**	**214**	**32**	**(50.0)**	**7**	**2**	**(6.7)**	**1**	**244**	**(31.5)**	**89**	**250**	**(26.5)**	**115**
Abscess, appendiceal	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Abscess, liver	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Acid regurgitation	26	(1.3)	6	0	(0.0)	0	0	(0.0)	0	7	(0.9)	2	6	(0.6)	0
Anorexia	9	(0.5)	3	1	(1.6)	0	0	(0.0)	0	9	(1.2)	0	7	(0.7)	1
Ascites	2	(0.1)	0	2	(3.1)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Atony, gastric	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Biliary disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Candidiasis, oral	17	(0.9)	9	1	(1.6)	0	0	(0.0)	0	10	(1.3)	9	18	(1.9)	13
Cholecystitis	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cholelithiasis	3	(0.2)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	1	(0.1)	0
Colitis	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Constipation	70	(3.6)	7	6	(9.4)	0	0	(0.0)	0	42	(5.4)	6	29	(3.1)	2
Diarrhea	189	(9.7)	107	8	(12.5)	3	2	(6.7)	1	94	(12.1)	54	92	(9.8)	56
Diarrhea, *Clostridium difficile* associated	7	(0.4)	6	0	(0.0)	0	0	(0.0)	0	2	(0.3)	2	2	(0.2)	0
Dilation, stomach	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Distention, intestinal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dry lips	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Dry mouth	11	(0.6)	6	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	11	(1.2)	8
Duodenitis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Dyspepsia	21	(1.1)	7	1	(1.6)	0	1	(3.3)	0	5	(0.6)	2	15	(1.6)	1
Dysphagia	5	(0.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Edema, tongue	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Enterocolitis, pseudomembranous	2	(0.1)	2	1	(1.6)	1	0	(0.0)	0	0	(0.0)	0	3	(0.3)	2
Erosive esophagitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Esophagitis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Fecal abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	2	0	(0.0)	0
Fecal occult blood	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Fistula, abdominal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Fistula, intestinal	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Fistula, perianal, infected	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Flatulence	9	(0.5)	2	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	7	(0.7)	4
Gallbladder disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Gastritis	4	(0.2)	1	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	5	(0.5)	0
Gastroenteritis, infectious	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Gastroesophageal reflux	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Glossitis	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hematemesis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hematochezia	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0

Hemorrhage, anal/rectal	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Hemorrhage, gastrointestinal	6	(0.3)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0
Hemorrhoids	6	(0.3)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hepatomegaly	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ileus	6	(0.3)	0	2	(3.1)	0	0	(0.0)	0	13	(1.7)	0	2	(0.2)	0
Incontinence, fecal	2	(0.1)	1	1	(1.6)	0	0	(0.0)	0	4	(0.5)	1	1	(0.1)	0
Infection, abdominal wall	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	0	(0.0)	0
Infection, dental process	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, intra-abdominal	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	16	(2.1)	1	8	(0.8)	1
Intubation, gastric, complication	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Intubation, gastrointestinal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Jaundice	4	(0.2)	1	0	(0.0)	0	0	(0.0)	0	3	(0.4)	2	1	(0.1)	0
Lesion, tongue	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Leukoplakia, oral	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Liver disorder	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Liver function abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Melena	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Nausea	142	(7.3)	61	10	(15.6)	2	0	(0.0)	0	67	(8.7)	26	70	(7.4)	31
Neoplasm, liver, metastatic	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, tongue, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Obstruction, bile duct	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Obstruction, intestinal	2	(0.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	1	(0.1)	0
Pain, anal/rectal	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Pain, mouth	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	1
Pancreatitis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Parotitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Perforation, intestinal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	1	(0.1)	0
Peritonitis	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	0
Stenosis, pyloric	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Stomatitis	8	(0.4)	2	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	1
Stomatitis, aphthous	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Surgery, intestinal, complication	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Thirst	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Ulcer, gastric	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Ulcer, mouth	3	(0.2)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	1
Varices, esophageal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Vomiting	76	(3.9)	22	3	(4.7)	0	0	(0.0)	0	41	(5.3)	13	38	(4.0)	11

(From Reference 46, September 21, 2001 submission)

7.2.12.5 Metabolic/Nutritional

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

Primaxin I.V. -In the "Adverse Reactions" section of the label there are no specific references to adverse events related to the metabolic/nutritional system.

Merrem I. V. - In the "Adverse Reactions" section of the label, adverse events related to the metabolic/nutritional system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: peripheral edema and hypoxia.

The following table displays adverse events related to the metabolic/nutritional 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: ***The clinical drug-related and non-drug-related adverse events related to the metabolic/nutritional 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 added to the "Adverse Laboratory Changes" section: acidosis (0.4%), hyperglycemia (0.3%), hypoglycemia (0.3%), and hypokalemia (0.3%).

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Number (%) of Patients With Metabolic/Nutritional System Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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
Metabolic, Nutritional, Immune	**55**	**(2.8)**	**4**	**9**	**(14.1)**	**0**	**0**	**(0.0)**	**0**	**17**	**(2.2)**	**1**	**38**	**(4.0)**	**3**
Acidosis	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	4	(0.4)	0
Alkalosis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Allergy	3	(0.2)	3	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	2
Allergy, food	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Anaphylaxis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Carbon dioxide increased	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dehydration	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	2	(0.3)	0	9	(1.0)	1
Electrolyte imbalance	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Fluid overload	1	(0.1)	0	4	(6.3)	0	0	(0.0)	0	1	(0.1)	0	4	(0.4)	0
Gout	7	(0.4)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Hypercholesterolemia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hyperglycemia	6	(0.3)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	5	(0.5)	0
Hypernatremia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypoglycemia	5	(0.3)	1	2	(3.1)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	0
Hypokalemia	6	(0.3)	0	2	(3.1)	0	0	(0.0)	0	3	(0.4)	0	6	(0.6)	0
Hypomagnesemia	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hypovolemia	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Iron deficiency	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Nutritional abnormality	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Weight loss	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0

(From Reference 46, September 21, 2001 submission)

7.2.12.6 Hematologic

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

Primaxin I.V. -In the "Adverse Reactions" section of the label, hematologic adverse events that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, and hemolytic anemia. Laboratory changes related to the hematopoetic system that were reported in the label without regard to drug relationship included: increased eosinophils, positive Combs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, and increased basophils.

Merrem I. V. - In the "Adverse Reactions" section of the label, hematologic adverse events that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: anemia. Laboratory changes related to the hematopoetic system that were reported in the label without regard to drug relationship included: increased platelets, increased eosinophils, prolonged prothrombin time, prolonged partial thromboplastin time, decreased platelets, positive direct or indirect Coombs test, decreased hemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time, and shortened partial thromboplastin time.

The following table displays adverse events, reported by Investigators, related to the hematopoetic 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: ***The clinical drug-related and non-drug-related adverse events related to the hemic and lymphatic system occurred at similar rates between the ertapenem 1 gm group and combined comparator group. However, in the tables of "Clinically Significant Laboratory Abnormalities", absolute neutrophil count <1000 cells/uL occurred at a greater frequency in the ertapenem 1 gm group (see section 7.2.9 for MO's discussion). Given that Dr. Seethaler, the Pharmacology/Toxicology Reviewer, concluded from available preclinical data that the risk of neutropenia was significant, the MO feels that the rate of neutropenia occurring in the clinical studies should be specifically noted as a potential serious adverse reaction in the "Adverse Reactions" section of the label.***

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 added to the "Adverse Laboratory Changes" section: anemia (1.1%), neutropenia (0.1%), thrombocytopenia (0.1%), and thrombocytosis (0.2%).

Number (%) of Patients With Hemic and Lymphatic System Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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
Hemic and Lymphatic System	**39**	**(2.0)**	**3**	**2**	**(3.1)**	**0**	**0**	**(0.0)**	**0**	**11**	**(1.4)**	**0**	**14**	**(1.5)**	**0**
Anemia	21	(1.1)	0	1	(1.6)	0	0	(0.0)	0	5	(0.6)	0	6	(0.6)	0
Anemia, hemolytic	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Arterial pO_2 decreased	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Coagulation disorder	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Disseminated intravascular coagulopathy	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Eosinophilia	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Leukemia, lymphoid, chronic	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Leukocytosis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Lymphadenitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Lymphadenopathy	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neutropenia	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
pCO_2 increased	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Splenomegaly	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Thrombocytopenia	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Thrombocytosis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0

(From Reference 46, September 21, 2001 submission)

7.2.12.7 Respiratory

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

Primaxin I.V. -In the "Adverse Reactions" section of the label, adverse events related to the respiratory system that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: chest discomfort, dyspnea, hyperventilation, and thoracic spine pain.

Merrem I. V. - In the "Adverse Reactions" section of the label, the incidence of apnea (1.3%) was reported irrespective of the relationship to meropenem. Additional adverse events related to the respiratory system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: respiratory disorder, dyspnea, pleural effusion, asthma, cough increased, and lung edema.

The following table displays adverse events related to the respiratory 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: ***The clinical drug-related and non-drug-related adverse events related to the respiratory 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 added to the "Respiratory System" section: asthma (0.2%), bronchoconstriction (0.6%), cough (1.4%), pharyngeal discomfort (0.4%), dyspnea (1.7%), pleural effusion (1.3%), epistaxis (0.4%), hemoptysis (0.2%), hiccups (0.2%), hypoxemia (1.0%), pleuritic pain (0.4%), pharyngitis (1.0%), respiratory insufficiency (combined adverse experiences of respiratory distress, respiratory distress syndrome, respiratory failure, and respiratory insufficiency) (2.0%), and voice disturbance (0.2%).

Number (%) of Patients With Respiratory System Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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
Respiratory System	**279**	**(14.3)**	**12**	**17**	**(26.6)**	**1**	**5**	**(16.7)**	**0**	**107**	**(13.8)**	**2**	**138**	**(14.6)**	**7**
Abscess, lung	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Apnea	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Asthma	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Atelectasis	9	(0.5)	0	2	(3.1)	0	0	(0.0)	0	8	(1.0)	0	2	(0.2)	0
Bronchitis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	0
Bronchitis, chronic	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Bronchoconstriction	11	(0.6)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	0
Chest sound abnormality	9	(0.5)	0	3	(4.7)	0	0	(0.0)	0	9	(1.2)	0	3	(0.3)	1
Choking	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Chronic obstructive pulmonary disease	10	(0.5)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	9	(1.0)	0
Congestion, nasal	3	(0.2)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Congestion, pulmonary	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Congestion, respiratory	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0
Cough	28	(1.4)	1	1	(1.6)	0	0	(0.0)	0	13	(1.7)	0	5	(0.5)	0
Discomfort, pharyngeal	7	(0.4)	2	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	1
Dry nose	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	1
Dry throat	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Dyspnea	33	(1.7)	3	4	(6.3)	1	1	(3.3)	0	14	(1.8)	0	23	(2.4)	2
Dyspnea, exertional	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Edema, pulmonary	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	2	(0.2)	0
Effusion, pleural	25	(1.3)	0	4	(6.3)*	0	0	(0.0)	0	12	(1.6)	0	18	(1.9)	0
Empyema	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Epistaxis	8	(0.4)	1	1	(1.6)	0	0	(0.0)	0	5	(0.6)	2	3	(0.3)	0
Hemoptysis	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0
Hiccups	3	(0.2)	0	2	(3.1)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0
Hypoventilation	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Hypoxemia	20	(1.0)	0	1	(1.6)	0	0	(0.0)	0	7	(0.9)	0	4	(0.4)	0
Infection, respiratory	3	(0.2)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Infection, respiratory, lower	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Infection, respiratory, upper	12	(0.6)	0	1	(1.6)	0	0	(0.0)	0	7	(0.9)	0	7	(0.7)	0
Infiltrate, pulmonary	3	(0.2)	0	1	(1.6)	0	1	(3.3)	0	1	(0.1)	0	1	(0.1)	0
Influenza	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Irritation, nasal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Laryngitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Lung volume decreased	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Mass, mediastinum	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Murmur, respiratory	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, lung	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, lung, malignant	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Nodule, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

Obstruction, airway	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Obstruction, nasal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Orthopnea	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Pain, pleuritic	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	4	(0.4)	0	
Pharyngitis	19	(1.0)	0	2	(3.1)	0	0	(0.0)	0	11	(1.4)	0	6	(0.6)	0	
Pleural disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Pleurisy	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0	
Pneumonia	28	(1.4)	1	2	(3.1)	0	2	(6.7)	0	9	(1.2)	0	15	(1.6)	0	
Pneumonia, aspiration	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Pneumonia, bacterial	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0	
Pneumothorax	6	(0.3)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0	
Radiodensity, pulmonary	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0	
Rales/rhonchi	15	(0.8)	1	2	(3.1)	0	0	(0.0)	0	8	(1.0)	0	9	(1.0)	0	
Respiratory distress	10	(0.5)	0	4	(6.3)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0	
Respiratory distress syndrome	8	(0.4)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	3	(0.3)	0	
Respiratory failure	14	(0.7)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	7	(0.7)	0	
Respiratory insufficiency	7	(0.4)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0	
Respiratory symptom improvement	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Rhinitis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Rhinitis, allergic	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Rhinorrhea	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0	
Secretion, bronchial	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Sinus disorder	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	1	
Sinusitis	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	3	(0.3)	0	
Sleep apnea	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Sputum, altered	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Sputum, purulent	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	0	(0.0)	0	
Tachypnea	8	(0.4)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0	
Tonsillitis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	
Tuberculosis, pulmonary	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0	
Voice disturbance	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	
Wheezing	15	(0.8)	1	1	(1.6)	0	3	(3.3)	0	8	(1.0)	0	9	(1.0)	0	

(From Reference 46, September 21, 2001 submission)

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7.2.12.8 Urogenital

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

Primaxin I.V. -In the "Adverse Reactions" section of the label, adverse events related to the urogenital system that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: acute renal failure, oliguria/anuria, polyuria, and urine discoloration. Laboratory changes related to the urogenital system that were reported in the label without regard to drug relationship included: decreased serum sodium, increased potassium, increased chloride, increased BUN, increased creatinine, and presence of urine protein, red blood cells, white blood cells, urine casts, bilirubin, and urobilinogen.

Merrem I. V. - In the "Adverse Reactions" section of the label, adverse events related to the urogenital system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: dysuria, kidney failure, vaginal moniliasis, and urinary incontinence. Laboratory changes related to the urogenital system that were reported in the label without regard to drug relationship included: increased creatinine and increased BUN.

The following table displays adverse events related to the urogenital 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: *The clinical drug-related and non-drug-related adverse events related to the urogenital system occurred at similar rates between the ertapenem 1 gm group and combined comparator group. As was previously discussed in section 7.2.11.6 of this review, pregnancy occurred in one patient (MK-0826 1 gm group) and the pregnancy resulted in a spontaneous abortion. Due to the severity of this adverse event, the preclinical findings reported by Dr. Seethaler, and the lack of additional data relating to pregnancy outcome in humans, the MO feels that this serious adverse event should be specifically noted in the label.*

Clinically significant laboratory adverse events related to the urogenital system occurred at similar rates 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 added to the "Urogenital System" section: abortion (0.1%), bladder dysfunction (0.2%), vaginal candidiasis (0.2%), hematuria (0.3%), oliguria/anuria (0.4%), vaginal pruritus (0.4%), renal insufficiency (combined adverse experiences of renal insufficiency and acute renal insufficiency) (0.8%), urinary retention (0.3%), vaginitis (1.3%), and vulvovaginitis (0.2%).

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Number (%) of Patients With Urogenital System Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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
Urogenital System	**146**	**(7.5)**	**40**	**11**	**(17.2)**	**1**	**0**	**(0.0)**	**0**	**66**	**(8.5)**	**7**	**86**	**(9.1)**	**28**
Abortion	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Bacteriuria	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Benign prostatic hypertrophy	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Bladder disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Bladder dysfunction	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Bleeding, genital	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Breast-feeding, use during	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	3	(0.3)	3
Candidiasis, vaginal	3	(0.2)	2	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Candiduria	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cervicitis	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cyst, kidney	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cyst, ovarian	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Cystitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Discharge, vaginal	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Diuresis decreased	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dryness, vaginal	1	(0.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dysuria	9	(0.5)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Edema, penis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	5	(0.5)	0
Epididymitis	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Galactorrhea	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Gynecomastia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hematuria	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hemorrhage, uterine	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	5	(0.5)	0
Hemorrhage, vaginal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Hot flashes	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	1	(0.1)	0
Hydronephrosis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	1	(0.1)	1
Infection, pelvic	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Infection, urinary tract	16	(0.8)	2	2	(3.1)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	1
Labor abnormality	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	10	(1.3)	1	11	(1.2)	0
Mastitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, cervical, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Neoplasm, prostate, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neoplasm, vaginal, malignant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Nocturia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Obstruction, prostate	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Obstruction, urinary tract	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Oliguria/anuria	8	(0.4)	0	3	(4.7)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pain, bladder	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	9	(1.2)	0	2	(0.2)	0
Pain, vaginal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Peritonitis, pelvic	2	(0.1)	1	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
Pruritus, vaginal	7	(0.4)	6	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	3	(0.3)	2
Pyelonephritis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Renal insufficiency	12	(0.6)	1	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	2	(0.2)	0
Renal insufficiency, acute	3	(0.2)	1	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	4	(0.4)	0
Residual urine	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Surgery, perineal	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Trauma, urethra	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ulcer, penis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Urethralgia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Urinary frequency	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	0
Urinary incontinence	4	(0.2)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	6	(0.6)	0
Urinary retention	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	7	(0.9)	0	4	(0.4)	0
Urinary urgency	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	0
Urination disorder	3	(0.2)	0	1	(1.6)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Urolithiasis	5	(0.3)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	4	(0.4)	0
Vaginitis	26	(1.3)	22	1	(1.6)	1	0	(0.0)	0	4	(0.5)	3	18	(1.9)	17
Vulvar disorder	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Vulvitis	2	(0.1)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Vulvovaginitis	4	(0.2)	2	0	(0.0)	0	0	(0.0)	0	2	(0.3)	1	2	(0.2)	2

(From Reference 46, September 21, 2001)

7.2.12.9 Dermatologic

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

Primaxin I.V. -In the "Adverse Reactions" section of the label, rash (0.9%), pruritus (0.3%), and urticaria (0.2%), were reported as possibly, probably, or definitely related to imipenem. Additional adverse events related to the dermatologic system that were reported as possibly, probably or definitely drug related occurring in less than 0.2% of patients included: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, and pruritus vulvae. Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with imipenem 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 infection (0.1%).

Merrem I. V. - In the "Adverse Reactions" section of the label, the incidence of rash (1.7%) and pruritus (1.6%) were reported irrespective of the relationship to meropenem. Additional adverse events related to the dermatologic system that were reported in greater than 0.1% but less than 1.0% of patients irrespective of relationship to meropenem included: urticaria, sweating, and skin ulcer. Adverse local clinical reactions that were reported irrespective of the relationship to therapy with meropenem were: inflammation at the injection site (2.4%), injection site reaction (0.9%), phlebitis/thrombophlebitis (0.8%), pain at the injection site (0.4%), and edema at the injection site (0.2%).

The following table displays adverse events, reported by Investigators, related to the dermatologic 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: ***The clinical drug-related and non-drug-related adverse events related to the dermatologic system occurred at similar rates between the ertapenem 1 gm group and combined comparator group. Rates were also similar to those reported historically in the imipenem and meropenem labels.***

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 added to the "Skin & Skin Appendage" section: dermatitis (0.3%), desquamation (0.2%), erythema (1.4%), flushing (0.2%), pruritus (1.4%), rash (2.4%), sweating (0.6%), and urticaria (0.2%).

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Number (%) of Patients With Dermatologic Clinical Adverse Experiences (Incidence ≥1 % Ertapenem 1 gm Treatment Groups) 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)[‡‡]		
Skin and Skin Appendage	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**	**n**	**(%)**	**DR**
	222	**(11.4)**	**46**	**10**	**(15.6)**	**0**	**3**	**(10.0)**	**0**	**125**	**(16.1)**	**31**	**95**	**(10.1)**	**28**
Abscess	7	(0.4)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	1	(0.1)	0
Abscess, incision	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Abscess, sterile	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Alopecia	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cellulitis	7	(0.4)	1	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	2	(0.2)	0
Closure, wound	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Contusion	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Cyanosis	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	1	(0.1)	0
Dehiscence, wound	10	(0.5)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	0	1	(0.1)	0
Delay, wound healing	1	(0.1)	0	1	(1.6)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	0
Dermatitis	5	(0.3)	1	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	4	(0.4)	0
Dermatitis, contact	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1
Dermatomycosis	4	(0.2)	1	0	(0.0)	0	0	(0.0)	0	4	(0.5)	1	3	(0.3)	1
Desquamation	4	(0.2)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Discoloration, skin	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	1
Dry mucous membranes	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dry skin	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	1	0	(0.0)	0
Ecchymosis	8	(0.4)	0	0	(0.0)	0	0	(0.0)	0	6	(0.8)	1	5	(0.5)	0
Erythema	27	(1.4)	4	1	(1.6)	0	0	(0.0)	0	13	(1.7)	3	11	(1.2)	5
Excoriation	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Flushing	4	(0.2)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.2)	2
Folliculitis	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	0	(0.0)	0
Herpes simplex	14	(0.7)	1	0	(0.0)	0	0	(0.0)	0	3	(0.4)	0	11	(1.2)	4
Herpes zoster	6	(0.3)	0	0	(0.0)	0	1	(3.3)	0	0	(0.0)	0	0	(0.0)	0
Hidradenitis suppurativa	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, graft/implant	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, skin	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	4	(0.5)	0	1	(0.1)	0
Infection, soft tissue	4	(0.2)	0	0	(0.0)	0	0	(0.0)	0	7	(0.9)	0	0	(0.0)	0
Infection, ulcer, skin	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infection, wound	14	(0.7)	0	0	(0.0)	0	0	(0.0)	0	16	(2.1)	0	1	(0.1)	1
Infection, wound, postoperative	7	(0.4)	1	2	(3.1)	0	0	(0.0)	0	7	(0.9)	0	0	(0.0)	0
Infused vein complication	119	(6.1)	73	2	(3.1)	2	3	(10.0)	1	61	(7.9)	43	63	(6.7)	43
Laceration	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	5	(0.5)	0
Night sweats	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	2	(0.2)	0
Nodule, cutaneous	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Pallor	4	(0.2)	0	0	(0.0)	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
Pruritus	28	(1.4)	16	0	(0.0)	0	0	(0.0)	0	20	(2.6)	9	18	(1.9)	9
Pruritus ani	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	1	0	(0.0)	0
Pruritus vulvae	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0	1	(0.1)	1

Rash	46	(2.4)	22	0	(0.0)	0	1	(3.3)	0	24	(3.1)	14	14	(1.5)	6
Scabies	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.1)	0
Sweating	11	(0.6)	0	1	(1.6)	0	0	(0.0)	0	6	(0.8)	1	5	(0.5)	0
Texture change, skin	1	(0.1)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ulcer, decubitus	4	(0.2)	0	2	(3.1)	0	0	(0.0)	0	1	(0.1)	0	5	(0.5)	0
Ulcer, skin	5	(0.3)	0	1	(1.6)	0	0	(0.0)	0	3	(0.4)	0	0	(0.0)	0
Urticaria	3	(0.2)	0	0	(0.0)	0	0	(0.0)	0	3	(0.4)	1	1	(0.1)	0
Vesicle	2	(0.1)	0	0	(0.0)	0	0	(0.0)	0	2	(0.3)	0	2	(0.2)	1

(From Reference 46, September 21, 2001 submission)

7.12.3 Overall ISS Conclusion

Based on the Integrated Summary of Safety review, the Medical Officer recommends approval of ertapenem sodium 1 gm daily administered for up to 14 days intravenously or 7 days intramuscularly for the indications in which efficacy has been demonstrated. Based on data provided in the ertapenem NDA the following conclusions can be made:

- Overall, clinically significant clinical and laboratory adverse events and treatment-related adverse events, occurring in the study therapy and 14-day follow-up periods, for ertapenem 1 gm daily (intravenous or intramuscular administration) in the Phase II and III clinical studies were similar to those of the approved comparator drugs (piperacillin/tazobactam and ceftriaxone).
- Overall, the rates of serious clinical and laboratory adverse events and dropouts, occurring in the study therapy and 14-day follow-up periods, for ertapenem 1 gm daily (intravenous or intramuscular administration) in the Phase II and III clinical studies were similar to those of the approved comparator drugs (piperacillin/tazobactam and ceftriaxone).
- There was a non-statistically significant trend for a greater number of deaths in the ertapenem 1 gm group in the pivotal complicated intra-abdominal infections study (P017).
- The rate of seizures (combined adverse events of seizure disorder, seizure-focal, and seizure-grand mal) that occurred in the study therapy plus 14-day follow-up period was 0.5% for patients in the ertapenem 1 gm group and 0.1% for patients in the combined comparator group. The rate of drug-related seizures (combined adverse events of seizure disorder, seizure-focal, and seizure-grand mal) that occurred in the study therapy plus 14-day follow-up period was 0.2% for patients in the ertapenem 1 gm group and 0.1% for patients in the combined comparator group. Based on a comparison with historical rates for "seizure" as an adverse event, ertapenem appears to fall between imipenem and meropenem as regards to the frequency of seizures reported overall or as drug-related, with imipenem reported to have the highest frequencies and meropenem the lowest.
- Regarding other adverse events commonly reported for beta-lactam antimicrobials, the incidence of rash, diarrhea, C. difficile associated disease, nausea, vomiting, and headache were similar for ertapenem 1 gm and comparator drugs.
- Based on review of clinically significant laboratory abnormalities occurring during the study therapy plus 14-day follow-up period, AST increase and absolute neutrophil count <1800 cells/uL and <1000 cells/uL were slightly more common in the ertapenem 1 gm group, but in general changes were transient and did not result in clinically significant adverse events.
- Intravenous infusion of ertapenem 1 gm is generally well tolerated for up to 14 days with respect to local tolerability in comparison to ceftriaxone and piperacillin/tazobactam.
- Intramuscular administration of ertapenem 1 gm is generally well tolerated with respect to local tolerability in comparison to ceftriaxone 1 gm.
- Ertapenem appears to be well tolerated irrespective of gender, however, it should be noted that in the one female patient (in ertapenem 1 gm group) that was pregnant in

the clinical studies, a spontaneous abortion occurred after 6 days of ertapenem therapy.

- Adverse event rates, although higher overall, were comparable across all study drugs for patients greater than 65 years old and for patients with renal dysfunction (Cr_{CL} <60 mL/min/1.73m^2).
- Adverse event rates were similar across all study drugs when examined by patient race.

Based on the Medical Officer's review of the Integrated Summary of Safety, the Medical Officer recommends the following additional information be provided by the Applicant as Phase IV commitments:

- A final study report for study 035, "A Randomized, Double-Blind, Parallel-Panel, Placebo-Controlled Study to Investigate the Effects of Maximum Plasma Concentrations of MK-0826 on QTc Interval Following Single IV Dose Administration in Healthy Subjects."
- A statistically adequate and well controlled study in patients with complicated intra-abdominal infections that compares death rate during the parenteral therapy period and at a 4 to 6 week follow-up visit.

The Medical Officer's recommendations for revisions to the "Warnings," "Precautions," and "Adverse Experiences" sections of the Applicant's proposed label are in Appendix 30.

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VIII. Dosing, Regimen and Administration Issues

Based on the demonstration of the non-inferiority of ertapenem to the FDA approved comparators utilized in the pivotal clinical studies, ertapenem 1 gm intravenously once daily appears to provide adequate antimicrobial coverage for the treatment of the requested indications. In Phase IIa studies and for a limited number of patients in the Applicant's Phase IIb intra-abdominal infections study (P017) doses of 1.5 gm and 2 gm once daily were evaluated; however, there did not appear to be an efficacy advantage at the higher doses and the incidence of both clinical and laboratory adverse experiences were higher. The efficacy of ertapenem doses less than 1 gm daily or for durations of therapy different than those studied in the Phase IIb/III clincal development program have not been investigated.

Based on Phase I studies, the bioavailability of ertapenem 1 gm administered intramuscularly is approximately 90% of the bioavailablilty of a dose of 1 gm administered intravenously over 30 minutes. Based on pharmacodynamic modeling, IM administration of ertapenem is predicted to provide adequate time above the MIC (MIC of 4.0 *u*g/mL) to adequately treat infections caused by sensitive organisms for the indications sought by the Applicant. While the Applicant has not provided a statistically adequate clinical study to demonstrate the efficacy of IM administration of ertapenem, they have provided a safety database for >100 patients (derived from P020, P021, and P029) that received IM ertapenem (as was agreed to at the End-of-Phase II meeting). The safety database supports the conclusion that ertapenem 1 gm IM once daily for up to 7 days is at least as well tolerated as ceftriaxone 1 gm IM once daily. For a full review of study 029 see Appendix 29.

The pharmacokinetics of a single 1 gm dose of ertapenem administered intravenously were investigated in 26 adult subjects with varrying degrees of renal impairment. Based on the results of this study the Applicant has proposed, and the FDA Clinical Pharmacology/ Biopharmaceutics review team has agreed, that the dose of ertapenem should be reduced to 500 mg once daily in patients with creatinine clearance ≤30 mL/min/1.73 m^2. Because approximately 30% of the dose is removed by a 4-hour hemodialysis session, for patients on hemodialysis a supplementary 150 mg postdialysis dose is recommended if the ertapenem dose has been given within 6 hours prior to hemodialysis.

IX. Use in Special Populations

Gender, Age, Race Effect

The Applicant performed analyses on the pivotal Phase IIb/III studies according to the subgroups of gender, age, and race. Based on these analyses the efficacy of ertapenem was similar to comparator drugs for males and females, for patients aged <65 years or ≥65 years, and for "Caucasian" and "Hispanic" patients. For "Black," "Mestizo," and "Other" patients there was a trend (based on point estimates) for greater efficacy in the ertapenem group. The following table displays the overall efficacy response by gender, age, and race.

Overall Primary Efficacy Response[†]
In the Primary Efficacy Population[‡]

	Ertapenem (N = 1171)		Comparator (N= 1038)	
	n/m	(%)	n/m	(%)
By Gender				
Female	560/619	(90.5)	486/547	(88.8)
Male	485/552	(87.9)	432/491	(88.0)
By Age				
<65 years	794/878	(90.4	687/774	(88.8)
≥65 years	251/293	(85.7)	231/264	(87.5)
By Race				
Caucasian	555/636	(87.3)	483/544	(88.8)
Black	128/140	(91.4)	108/126	(85.7)
Hispanic	265/290	(91.4)	232/259	(89.6)
Mestizo	68/73	(93.2)	69/77	(89.6)
Other[§]	29/32	(90.6)	26/32	(81.3)

[†] The primary efficacy response displayed is the clinical response in Skin and Skin Structure Infections, Pelvic Infections, and Community-Acquired Pneumonia, the microbiological response in Urinary Tract Infections, and the combined clinical and microbiological response in Intra-abdominal Infections.
[‡] The primary efficacy population used was the clinically evaluable population in Skin and Skin Structure Infections, Pelvic Infections, and Community-Acquired Pneumonia, and the microbiologically evaluable population in Urinary Tract Infections and Intra-abdominal Infections.
[§] Other includes Latin American, Asian, Philippina, Indian, Spanish, Polynesian, Mexican, Mulatto, Spanish American, Colored, Armenian, Maori, Mixed, Hispanic/White, African, and not specified.
N = Total number of patients in the treatment group.
n/m = Number of patients with favorable response in category/number of patients in category.
(Compiled from Applicant's Tables D-46, D-47, and D-48, Volume 1 of 22)

With the exception of nausea and vomiting, which occurred more frequently in females, the incidence of clinical and laboratory adverse experiences were similar in males and females.

The overall patterns of clinical adverse experiences and laboratory adverse experiences were generally similar for patients ≥65 years and <65 years. As might be expected in an older population that has a greater number of co-morbid conditions and a higher frequency of concommitant medication use, the frequencies of adverse experiences were

often increased. However, the increased frequencies of specific adverse events appeared to be balanced across the ertapenem 1 gm and combined comparator groups, signifying that no signal was present in the data base to suggest that ertapenem specific drug toxicity was increased in patients ≥65 years old.

The incidence of clinical adverse experiences were similar across racial groups for the ertapenem 1 gm and comparator groups. The majority of laboratory adverse experiences were also similar across groups with the exception of a slightly higher incidence of AST >5x ULN in "Hispanic" patients and ANC <1000 cells/uL in "Other" patients in the ertapenem 1 gm group. However, within the Applicant's "Other" group, it did not appear that one specific race was at increased risk of ANC <1000 cells/uL.

Pediatric Program

The Applicant submitted plans for a Pediatric Development Program and a prompt for a Written Request for Pediatric Studies. In response, the Agency issued a Written Request for Pediatric Studies (WR) to the Applicant in May, 2000. The WR requested that the Applicant perform a total of five studies in pediatric patients aged 3 months through 17 years. Based on the protein binding characteristics of ertapenem, the Agency concurred with the Applicant that its use in patients <3 months may result in significant displacement of bilirubin from albumin resulting in kernicterus. Therefore the requirement to study pediatric patients <3 months old has been waived. The five studies requested in the WR included:

Study 1: An open-label, intravenous study to evaluate the plasma concentration profiles of MK-0826 in pediatric patients

Study 2: An open-label, multicenter study to evaluate the cerebrospinal fluid concentration profile of MK-0826 after intravenous administration in pediatric patients with meningitis

Study 3: A prospective, multicenter, randomized, comparative study to evaluate the safety, local tolerability and clinical outcome of MK-0826 versus comparator (to be named) in pediatric patients with hospital acquired pneumonia, intra-abdominal infection, or acute pelvic infection

Study 4: A prospective, multicenter, double-blind, randomized, comparative study to evaluate the safety, local tolerability and clinical outcome of MK-0826 versus ceftriaxone sodium in pediatric patients with community acquired pneumonia, complicated urinary tract infection, or skin infection

Study 5: A prospective, multicenter, randomized, comparative study to evaluate the safety, local tolerability and efficacy of MK-0826 versus comparator (to be named) in pediatric patients for the treatment of acute bacterial meningitis

The Applicant has recently completed Study 1. Protocols for studies 2, 3, and 4 have been submitted to the FDA for review and these studies are currently ongoing or expected to begin enrollment shortly. Per the WR, reports of the above studies must be submitted to the Agency on or before November 30, 2004.

Renal Impairment

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 function (<60 mL/min/1.73 m^2); however, as might be expected in a population with impaired renal function with a greater 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, it is unlikely that ertapenem specific drug toxicity was increased in patients with creatinine clearance <60 mL/min/1.73 m^2.

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. At the Medical Officer's request the Applicant performed an analysis of adverse experiences by degree of hepatic impairment (Child-Pugh class) for patients enrolled in the Phase II and III studies. These analyses were submitted on October 1, 2001. The overall patterns of clinical adverse experiences and laboratory adverse experiences were generally similar for patients with hepatic impairment; however, as might be expected in a population of patients with hepatic impairment and a greater 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, it is unlikely that ertapenem specific drug toxicity was increased in patients with hepatic impairment.

Use in Pregnancy

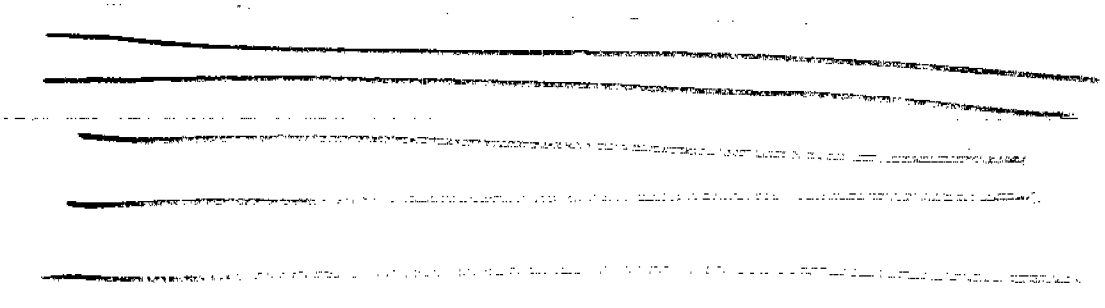
No clinical studies regarding use of ertapenem in pregnancy have been performed. For details of pregnancy outcome in the one pregnant patient that received ertapenem in the Applicant's clinical development program please see section 7.2.11.6 of this review.

X. Conclusions and Recommendations

Provided a label can be agreed upon between representatives of Merck and ODE IV, the Medical Officer recommends that an approval be granted for ertapenem for the indications of: complicated intra-abdominal infections, skin and skin structure infections, community acquired pneumonia, complicated urinary tract infections including pyelonephritis, and acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections.

Based on the available efficacy and safety data, the benefit of ertapenem as a therapeutic antimicrobial for the above indications outweighs the risks of administration. In the Applicant's clinical studies, the overall toxicity profile of ertapenem was similar to that of the β-lactam antimicrobials (piperacillin/tazobactam and ceftriaxone) to which it was compared with one notable exception. A higher percentage of deaths occurred in the ertapenem 1 gm group than in the comparator group in the complicated intra-abdominal study. Although, this finding is potentially explainable by a greater severity of illness in the ertapenem group, until more data are available the "Adverse Reactions" section of the label should reflect this important finding. In addition, the Medical Officer recommends that the Applicant perform, as a Phase IV commitment, a double-blind, randomized, statistically adequate study that assesses the death rate at the end of parenteral therapy and at 28 days post therapy in adult patients with complicated intra-abdominal infections.

While carbapenems have not historically been associated with intracardiac conduction delays, the Applicant has not provided the final results of their recently completed Phase I study (P035) that addresses this issue in subjects receiving ertapenem. Therefore the Medical Officer recommends that submission of the final study report for P035 be required as an additional Phase IV commitment.



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IX. Appendices

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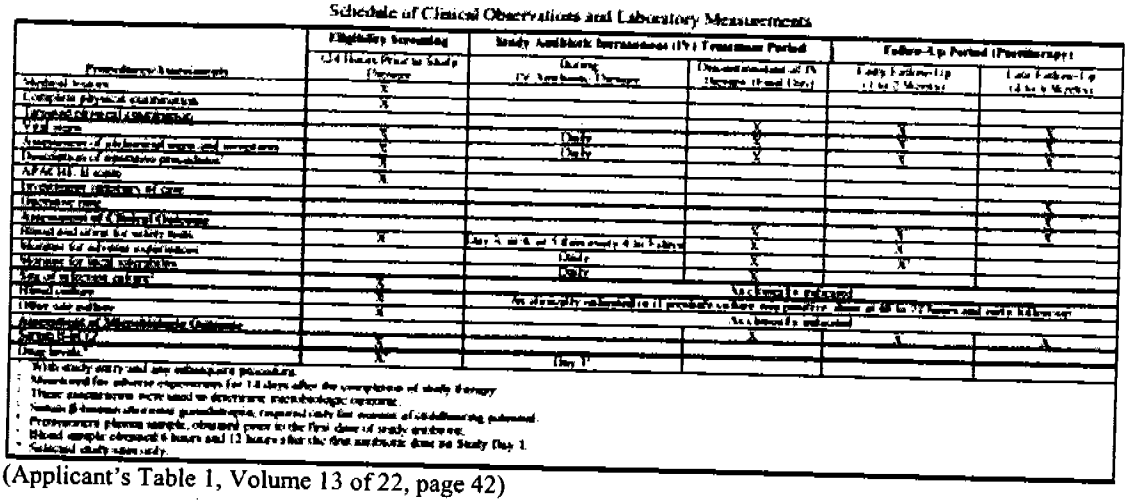
Appendix 1

Protocol 017

Schedule of Clinical Observations and Laboratory Measurements



(Applicant's Table 1, Volume 13 of 22, page 42)

Appendix 2

Protocol 017

Patient Accounting
(Randomized Population)

	MK-0826 1 g	MK-0826 1.5 g	Piperacillin/ Tazobactam	Total
ENTERED	323	14	328	665
Male (age range)	193 (17 to 87)	11 (20 to 79)	206 (17 to 87)	410 (17 to 87)
Female (age range)	130 (18 to 92)	3 (48 to 72)	122 (18 to 92)	255 (18 to 92)
COMPLETED THERAPY	264	9	271	544
DISCONTINUED THERAPY	59	5	57	121
Clinical adverse experience	17	0	18	35
Laboratory adverse experience	1	0	2	3
Lost to follow-up	0	0	0	0
Deviation from protocol	6	0	8	14
Withdrew from study	3	1	1	5
Inclusion/exclusion criteria not met	9	0	5	14
Clinical/microbiologic failure	12	2	19	33
Patient withdrew consent	4	1	4	9
Clinical trial terminated	1	0	0	1
Pathogen resistant	3	0	0	3
Death	2	1	0	3
Personal reasons	1	0	0	1
COMPLETED STUDY	256	10	248	514
DISCONTINUED STUDY	67	4	80	151
Clinical adverse experience	17	0	23	40
Laboratory adverse experience	1	0	1	2
Lost to follow-up	15	0	11	26
Deviation from protocol	3	0	7	10
Withdrew from study	1	1	1	3
Inclusion/exclusion criteria not met	7	0	3	10
Clinical/microbiologic failure	13	1	30	44
Patient withdrew consent	4	1	4	9
Pathogen resistant	1	0	0	1
Death	4	1	0	5
Personal reasons	1	0	0	1

(Applicant's Table 9, Volume 13 of 22, page 80)

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Patient Accounting
(Microbiologically Evaluable Population)

	MK-0826 1 g	MK-0826 1.5 g	Piperacillin/ Tazobactam	Total
ENTERED:	203	7	207	417
Male (age range)	133 (17 to 87)	4 (20 to 73)	137 (17 to 85)	274 (17 to 87)
Female (age range)	70 (18 to 89)	3 (48 to 72)	70 (18 to 89)	143 (18 to 89)
COMPLETED THERAPY	190	7	190	387
DISCONTINUED THERAPY	13	0	17	30
Clinical adverse experience	7	0	6	13
Laboratory adverse experience	0	0	1	1
Lost to follow-up	0	0	0	0
Deviation from protocol	0	0	0	0
Clinical/microbiologic failure	5	0	10	15
Patient withdrew consent	1	0	0	1
COMPLETED STUDY	192	7	183	382
DISCONTINUED STUDY	11	0	24	35
Clinical adverse experience	8	0	4	12
Laboratory adverse experience	0	0	1	1
Lost to follow-up	0	0	0	0
Deviation from protocol	0	0	0	0
Clinical/microbiologic failure	2	0	19	21
Patient withdrew consent	1	0	0	1

(Applicant's Table 10, Volume 13 of 22, page 81)

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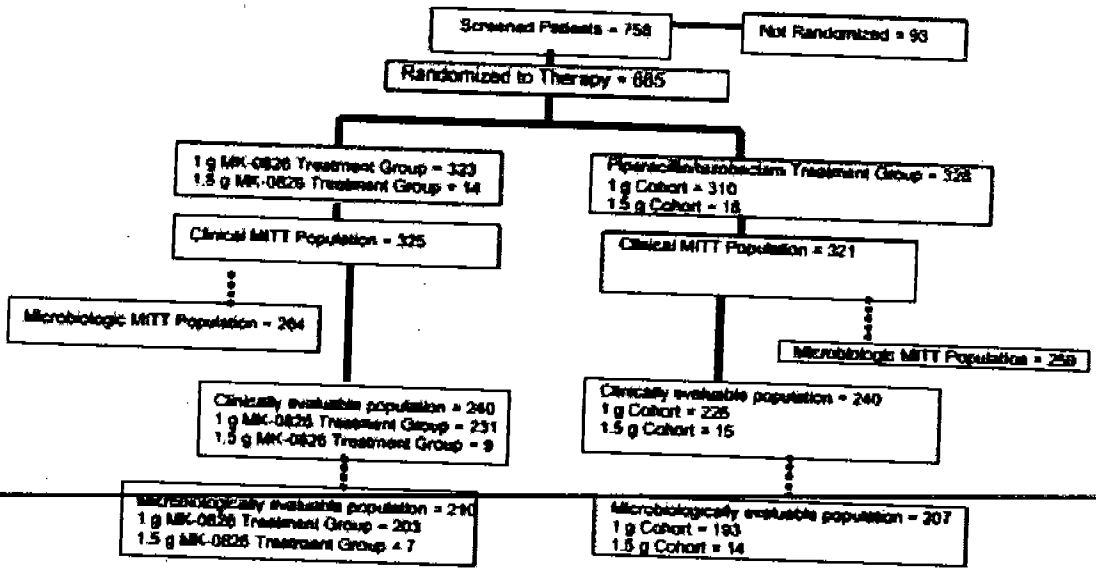
Appendix 3

Protocol 017

Profile of Patient Enrollment



(Applicant's Figure 1, Volume 13 of 22, page 90)

Protocol 017

Appendix 4

Summary of Patients For Whom Evaluabilty and/or Outcome Changes Were Made By the Medical Officer

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Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
MK-0826 1 gm																
o	0180	Y	Y	Y	Y	Y	Y	Y	Y	1	0	1	0	1	0	Patient was discontinued from study drug for both confusion and wound infection, which occurred concurrently, and received additional non-study antibiotic therapy. Therefore the MO considered the patient to have an outcome of failure.
o	0196	Y	Y	Y	Y	N	N	N	N	1	0	1	0	1	0	Patient received 29 days of study drug therapy and an additional day of non-study antibiotic therapy. Since the patient required more than 120% duration of study therapy and additional antimicrobial the MO considered the patient outcome to be failure.
o	0248	Y	Y	N	N	Y	Y	N	N	1	0					Entry culture did not contain pathogen susceptible to study antibiotics. Patient readmitted with UGI bleed and fever, no source documented and treated with empiric antibiotics. Therefore MO considered patient evaluable with failure outcome (potential bleed due to infection erroding at original surgical site).
e,o	0250	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Although TOC visit was several days out of window the CRF form for visit noted that the patient had received a non-study antibiotic for a wound infection the prior week, which would have occurred within window. Therefore the MO considered the patient evaluable with failure outcome.
e	0285	Y	Y	Y	Y	N	Y	N	Y	0	0	0	0	0	0	Patient considered unevaluable by Applicant due to baseline intercurrent medical event. MO did not appreciate any such event in the CRF. Therefore the MO considered the patient evaluable.
e,o	0287	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient received non-study antibiotic prior to FU for treatment of UTI. Therefore the MO considered patient unevaluable with indeterminate outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
o	0418	Y	Y	Y	Y	Y	Y	Y	Y	1	0	1	0	1	0	Patient was treated for wound infection for 2-3 days with nonstudy antibiotic by private MD. Investigator did not see patient until 6 days later and felt patient had not needed antibiotic. MO did not feel private MDs opinion could be ignored and considered outcome to be failure.
e,o	0475	Y	Y	N	N	Y	N	N	N	1	1					Patient received course of non-study antibiotic for H.pylori prophylaxis prior to FU. Therefore MO considered patient clinically unevaluable (culture negative) with indeterminate outcome.
e,o	0517	Y	Y	Y	Y	Y	N	Y	N	0	1	1	1	0	1	Patient developed a superficial wound infection 4-5 days prior to discontinuing study drug that was being managed only with dressing changes, then developed pneumonia and was taken off study and placed on non-study antibiotics to treat pneumonia. Therefore MO considered patient unevaluable with indeterminate outcome.
o	0606	Y	Y	N	N	N	N	N	N	1	1					Patient was given course of non-study antibiotics concurrently with study drug. Therefore MO considered outcome as indeterminate.
e,o	0641	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient given oral non-study antibiotic at the end of IV study drug with no reason stated in discharge summary. Therefore MO considered it to be given for continued intra-abdominal coverage and considered the patient evaluable with failed outcome.
e,o	0719	Y	Y	N	N	Y	N	N	N	1	1					Patient given non-study antibiotics as UTI prophylaxis and treatment prior to FU. Therefore MO considered unevaluable with indeterminate outcome.
e,o	0925	Y	Y	Y	Y	Y	N	Y	N	1	1	1	1	1	1	Patient given non-study antibiotic for treatment of UTI prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	0961	Y	Y	Y	Y	Y	N	Y	N	1	1	1	1	1	1	Patient given non-study antibiotic for treatment of foot cellulitis prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
e,o	0965	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient given non-study antibiotic for treatment of UTI prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e	1660	Y	N	N	N	N	N	N	N	I	I					Patient had PID. Therefore MO did not considered patient met minimal disease definition to be included in MITT population.
o	5100	N	N	N	N	N	N	N	N	I	I					Patient received non-study antibiotic for treatment of UTI. Therefore MO considered patient to have indeterminate outcome.
e	5365	Y	Y	Y	Y	Y	N	Y	N	0	0	0	0	0	0	Patient received tobramycin while on study therapy and additional oral antibiotics as follow-up to study therapy. MO considered patient unevaluable prior to oral therapy due to concomitant Tobramycin with study therapy.
e,o	5418	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient received oral flagyl to treat *C.dificile* during course of study therapy. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5428	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient received multiple other non-study antibiotics for treatment of sinus infection and sepsis prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5433	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient received non-study antibiotics for the treatment of pneumonia prior to FU. Therefore the MO considered patient unevaluable with indeterminate outcome.
e,o	5456	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient discharged to NH on IV study drug and then readmitted to hospital for N/V and dehydration at which point they received one dose of ceftriaxone and the investigator took patient off study due to alternate antibiotic being given. Therefore MO considered patient unevaluable with indeterminate outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
e,o	5505	Y	Y	Y	Y	Y	N	Y	N	1	1	1	1	1	1	Patient given course of flagyl for *C.dificile* spanning IV study drug and FU period. Therefore MO considered patient unevaluable with indeterminate outcome.
o	5528	Y	Y	Y	Y	Y	Y	Y	Y	1	0	1	0	1	0	Patient was given non-study antibiotic for wound infection by family MD, which surgeon stopped several days latter. MO felt could not exclude true infection since surgeon did not see patient for several days. Therefore MO considered patient to be failure
e,o	5561	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient improved on study therapy, but sent home on oral antibiotics for continued intra-abdominal infection coverage. Therefore MO considered the patient evaluable with failure outcome.
e,o	5566	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient improved on study therapy, but sent home on oral antibiotic for continued treatment of intra-abdominal infection. Therefore MO considered patient evaluable with failure outcome.
e,o	5715	Y	Y	N	N	Y	N	N	N	1	1					Patient received non-study antibiotics for possible infected knee prior to FU. Therefore MO considered the patient unevaluable with indeterminate outcome.
e,o	5799	Y	Y	Y	Y	Y	N	Y	N	0	1	0	1	0	1	Patient removed from study and treated with alternative non-study antibiotics when found to have empyema. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5881	Y	Y	Y	Y	Y	N	Y	N	1	1	1	1	1	1	Patient given non study antibiotic (flagyl) for treatment of diarrhea prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
o	5988	Y	Y	Y	Y	N	N	N	N	1	1	1	1	1	1	Patient received non-study antibiotic during IV study period (3d flagyl) for diarrhea. Therefore MO considered patient unevaluable with indeterminate outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
MK-0826 1.5 gm																
e,o	5111	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient received alternate antibiotic therapy for a line infection prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e	5167	Y	Y	Y	Y	N	Y	N	Y	0	0		0		0	Applicant considered unevaluable due to baseline micro exclusion. Patient had Enterococcus spp., B. buccae, Lactobacillus spp. and C. albicans on entry peritoneal fluid culture. Since anaerobes generally would be expected to be sensitive, the MO considered patient evaluable.
Piperacillin/tazobactam																
e,o	0140	Y	Y	Y	Y	Y	N	Y	N	0	I	0	I	0	I	Patient was discontinued from study therapy due to acute renal failure and continued on alternate antimicrobial therapy. Since not discontinued due to failure, MO considered patient unevaluable with indeterminate outcome.
e,o	0172	Y	Y	Y	Y	N	Y	N	Y	I	0	I	0	I	0	Patient given additional oral antibiotic after study drug for "phlegmon prophylaxis". Therefore MO considered patient evaluable with failure outcome.
e,o	0181	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient was treated with non-study antibiotics prior to FU visit. Therefore the MO considered the patient unevaluable with indeterminate outcome.
o	0695	Y	Y	Y	Y	N	N	N	N	0	I	0	I	0	I	Patient was discontinued from study after 24 hours of therapy due to sepsis and acute renal failure requiring dialysis and placed on alternate antimicrobials. Since patient had not received 48 hours of therapy, the MO considered outcome as indeterminate.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
e,o	0963	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient received 4 days study therapy and then was discharged on two non-study oral antibiotics for prophylaxis against recurrence of intra-abdominal infection. Therefore MO considered patient evaluable with failure as outcome.
e,o	1268	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient given non-study antibiotic for treatment of dental infection prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5045 1.5 gm cohort	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient was given another patients antibiotic on the last day of study and can not determine how many doses of non-study antibiotic the patient received. The MO therefore considered the patient unevaluable with an indeterminate outcome.
e,o	5053 1.5 gm cohort	Y	Y	Y	Y	Y	N	Y	N	I	I	I	I	I	I	Patient developed pneumonia and was treated with alternate antibiotics before FU visit. Therefore MO considered unevaluable with indeterminate outcome.
e	5109 1.5 gm cohort	Y	Y	Y	Y	Y	N	Y	N	0	0	0	0	0	0	Patient initially had a CT guided aspiration/drainage procedure, but had to have subsequent surgery due to failure of the initial procedure. MO considered initial procedure inadequate therapy so MO considered patient unevaluable.
e	5250 1.5 gm cohort	Y	Y	Y	Y	Y	N	Y	N	0	0	0	0	0	0	Patient readmitted prior to FU with fever and sepsis and found to have retained common bile duct stone. Therefore MO considered initial surgery to be inadequate and patient to be unevaluable.
e,o	5333	Y	Y	N	N	Y	N	N	N	1	I					Patient developed pneumonia and was treated with non-study antibiotics prior to FU. Therefore the MO considered patient unevaluable with indeterminate outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
o	5342	Y	Y	Y	Y	N	N	N	N	1	I	1	I	1	I	Patient received non-study antibiotics prior to FU for treatment of UTI. Therefore MO considered patient to have indeterminate outcome.
e,o	5408	Y	Y	Y	Y	Y	N	Y	N	1	I	1	I	1	I	Patient got additional antibiotics for "post-graft" prophylaxis (>24 hours) prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5415	Y	Y	Y	Y	Y	N	Y	N	0	I	0	I	0	I	Patient was readmitted with SBO requiring additional surgery, but infection was not present at re-operation according to operative report. Patient got 6 days peri-op "prophylaxis" (ancef) and additional non-study antibiotic to treat UTI prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5422	Y	N	N	N	N	N	N	N	1	I					Patient did not meet criteria for complicated appendicitis. Patient received 2 courses of non-study antibiotics for strep throat and shoulder infection prior to FU. Therefore MO considered patient to have indeterminate outcome.
o	5520	Y	Y	Y	Y	N	N	N	N	1	I	1	I	1	I	Patient readmitted with SBO and got 2 days non-study antibiotics that Investigator says were given in error not due to infection. Therefore MO considered patients unevaluable with indeterminate outcome.
e,o	5536	Y	Y	N	N	Y	N	N	N	1	I					Patient received multiple non-study antibiotics for treatment of pneumonia prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
e,o	5560	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient was given non-study oral antibiotic following study drug for continued therapy of intra-abdominal infection. Therefore MO considered patient evaluable with failure outcome.
e,o	5564	Y	Y	Y	Y	N	Y	N	Y	1	0	1	0	1	0	Patient improved on study therapy, but sent home on oral antibiotics. Therefore MO considered patient evaluable with failure outcome.

Discrepancy in evaluability (e) and/or outcome (o)	AN	Applic Clin MITT	MO Clin MITT	Applic Micro MITT	MO Micro MITT	Applic Clin Eval	MO Clin Eval	Applic Micro Eval	MO Micro Eval	Applic Clin Outcome	MO Clin Outcome	Applic Micro Outcome	MO Micro Outcome	Applic Comb Outcome	MO Comb Outcome	MO Comment
e,o	5719	Y	Y	Y	Y	Y	N	Y	N	1	I	1	1	1	I	Patient received non-study antibiotic for treatment of pneumonia prior to FU. Therefore MO considers patient unevaluable with indeterminate outcome.
e	5760	Y	Y	Y	Y	Y	N	Y	N	0	0	0	0	0	0	Patient failed after initial procedure of percutaneous drainage, therefore MO considered initial procedure inadequate and patient unevaluable.
e,o	5896	Y	Y	Y	Y	Y	N	Y	N	1	I	1	I	1	I	Patient developed SBO (not thought to be infected), but received 3 days of assorted non-study antibiotics prior to FU. Therefore MO considered patient unevaluable with indeterminate outcome.
o	5975	Y	Y	Y	Y	N	N	N	N	0	I	0	I	0	I	Patient thought to have persistent infection and treated with non-study antibiotics but autopsy attributed death to PE and no mention of persistent infection. MO considered outcome indeterminate based on data provided in CRF.

e=evaluability change
o=outcome change
Y=evaluable
N=unevaluable
1=favorable outcome/cure
0=unfavorable outcome/failure
I=indeterminate outcome
Blank cell=no data available (considered indeterminate in analyses)

Protocol 017

Appendix 5

Patient Accounting of Evaluability
(Randomized Population)

Reasons Not Evaluable	MK-0826 1 g (N=323)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=328)	
	n	(%)	n	(%)	n	(%)
Clinical Protocol Evaluable Population						
Clinical protocol evaluable	231	(71.5)	9	(64.3)	240	(73.2)
Clinical protocol nonevaluable	92	(28.5)	5	(35.7)	88	(26.8)
Disease definition not met	8	(2.5)	0	(0.0)	10	(3.0)
Test-of-cure window violation	24	(7.4)	0	(0.0)	26	(7.9)
Inadequate/inappropriate study therapy	32	(9.9)	1	(7.1)	23	(7.0)
Prior antibiotics violation	6	(1.9)	1	(7.1)	7	(2.1)
Concomitant antibiotics violation	13	(4.0)	1	(7.1)	13	(4.0)
Baseline/intercurrent medical events	12	(3.7)	0	(0.0)	9	(2.7)
Baseline microbiology-resistant pathogen	6	(1.9)	1	(7.1)	7	(2.1)
Other	0	(0.0)	1	(7.1)	2	(0.6)
Inadequate surgical source control	9	(2.8)	0	(0.0)	13	(4.0)
Microbiologic Protocol Evaluable Population						
Microbiologic protocol evaluable	203	(62.8)	7	(50.0)	207	(63.1)
Microbiologic protocol nonevaluable	120	(37.2)	7	(50.0)	121	(36.9)
Not clinically evaluable	92	(28.5)	5	(35.7)	88	(26.8)
Baseline microbiology not performed/inadequate	5	(1.5)	0	(0.0)	1	(0.3)
Baseline microbiology-no pathogen isolated	47	(14.6)	3	(21.4)	53	(16.2)
Clinical MITT Population						
Clinical MITT evaluable	311	(96.3)	14	(100)	321	(97.9)
Clinical MITT nonevaluable	12	(3.7)	0	(0.0)	7	(2.1)
Patient did not receive at least 1 dose of study therapy	7	(2.2)	0	(0.0)	3	(0.9)
Minimal disease definition not met	3	(0.9)	0	(0.0)	3	(0.9)
Pharmacy dispensing errors preclude evaluability	2	(0.6)	0	(0.0)	1	(0.3)
Microbiologic MITT Population						
Microbiologic MITT evaluable	256	(79.3)	8	(57.1)	259	(79.0)
Microbiologic MITT nonevaluable	67	(20.7)	6	(42.9)	69	(21.0)
Not clinically MITT evaluable	12	(3.7)	0	(0.0)	7	(2.1)
Baseline microbiology not performed/inadequate	4	(1.2)	0	(0.0)	1	(0.3)
Baseline microbiology-no pathogen isolated	47	(14.6)	3	(21.4)	53	(16.2)
Follow-up microbiology inadequate	8	(2.5)	3	(21.4)	11	(3.4)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being nonevaluable, the patient was counted only once in the non-evaluable category.
MITT = Modified intent-to-treat approach.

(Applicant's Table 13, Volume 13 of 22, page 92)

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Appendix 6

Number of Patients Entered by Investigator and Treatment Group According to the Applicant (Randomized Population)

Study Number	Investigator	Location	MK-0826 1gm (N=323)			MK-0826 1.5 gm (N=14)			Piperacillin/ Tazobactam (N=328)		
			Enroll	Eval	% Eval	Enroll	Eval	% Eval	Eroll	Eval	% Eval
001	Simms, H. Hank	Providence, RI	5	1	20%	0	0	-	5	1	20%
002	Wilson, Eric	Orange, CA	5	3	60%	0	0	-	4	3	75%
003	Solomkin, Joseph S.	Cincinnati, OH	3	1	33%	0	0	-	1	0	-
004	Hassett, James M.	Buffalo, NY	14	9	64%	0	0	-	14	11	79%
005	Lucasti, Christopher	Somers Point, NJ	14	8	57%	4	3	75%	23	14	61%
006	Gilbert, David N.	Portland, OR	2	2	100%	0	0	-	2	1	50%
007	Yellin, Albert E.	Los Angeles, CA	26	12	46%	0	0	-	24	15	63%
008	Postier, Russell	Oklahoma City, OK	7	2	29%	0	0	-	9	7	78%
009	Harrison, Paul B.	Wichita, KA	3	3	100%	0	0	-	1	0	-
010	Bankey, Paul	Worcester, MA	1	0	-	1	0	-	1	0	-
011	Fulda, James Gerard	Newark, DE	5	1	20%	1	1	100%	6	3	50%
012	Klein, Stanley	Torrance, CA	15	9	60%	0	0	-	16	9	56%
013	Wittmann, Dietmar H.	West Milwaukee, WI	2	0	-	1	0	-	1	1	100%
014	Diebel, Larry	Detroit, MI	4	0	-	0	0	-	4	1	25%
015	Bennion, Robert C.	Sylmar, CA	2	2	100%	0	0	-	2	1	50%
016	Metzler, Michael H.	Columbia, MI	5	4	80%	0	0	-	4	2	50%
017	Mangiante, Eugene	Memphis, TN	2	2	100%	1	0	-	3	1	33%
019	Fry, Donald E.	Albuquerque, NM	8	4	50%	0	0	-	7	4	57%
022	Barie, Philip	New York, NY	2	1	50%	0	0	-	3	2	67%
023	Bauwens, Eric J.	Phoenix, AR	8	2		6	3	50%	14	10	71%
025	Messick, William Joseph/Miles, Scherer William	Charlotte, NC	0	0	-	0	0	-	1	1	100%
027	Christou, Nicholas V.	Canada	14	8		0	0	-	14	5	36%
029	Rotstein, Ori D.	Canada	5	3	60%	0	0	-	5	4	80%
030	Lew, Daniel Pablo	Switzerland	6	2	33%	0	0	-	3	2	67%
031	Lange, Jochen	Switzerland	4	4	100%	0	0	-	6	5	83%
032	Ocampo Gonzalez, Saul	Mexico	6	5	83%	0	0	-	5	3	60%
033	Velasquez Burgos, Juan	Colombia	5	3	60%	0	0	-	5	3	60%
034	Letelier, Luz Maria	Chile	9	5	56%	0	0	-	11	7	64%
035	Buechler, Markus W.	Switzerland	4	2	50%	0	0	-	3	3	100%
037	Jasovich, Abel	Argentina	4	1	25%	0	0	-	5	4	80%
038	Barboza, E.	Peru	11	10	91%	0	0	-	9	8	89%
039	Betancure Martinez, J	Columbia	2	2	100%	0	0	-	3	0	-
040	Ribas Filho, Jurandir	Brazil	22	18	82%	0	0	-	22	17	77%
041	Lunstedt, B.	Germany	2	2	100%	0	0	-	1	1	100%
043	Stratchounski, Leonid	Russia	9	7	78%	0	0	-	9	6	-
044	Vainrub, Bernardo	Venuzuela	1	1	100%	0	0	-	0	0	-
045	Ozier, Yves	France	3	2	67%	0	0	-	2	1	50%
046	Poisson, Michel	Canada	4	3	75%	0	0	-	3	2	67%
047	Bohnen, John M.A.	Canada	0	0	-	0	0	-	1	1	100%
048	Aoun, Michael	France	1	0	-	0	0	-	1	1	100%
049	Donini, Ippolito	Italy	3	1	33%	0	0	-	1	0	-
050	Salvestrini, Frances	Italy	2	0	-	0	0	-	3	0	-
051	Trignano, Mario	Italy	2	1	50%	0	0	-	3	2	67%
052	Du Toit, Roelof Step	South Africa	4	0	-	0	0	-	2	1	50%
053	Warren, Brian Leigh	South Africa	20	15	75%	0	0	-	21	15	71%
054	Brown, Jacqueline	South Africa	5	2	40%	0	0	-	5	1	20%
055	Alcaraz Lorente, Pat	Spain	1	1	100%	0	0	-	0	0	-
056	Balibrea, Jose Luis	Spain	0	0	-	0	0	-	1	0	-
058	Gonzalez, Javier	Spain	2	2	100%	0	0	-	2	2	100%
059	Tellado, Jose Maria	Spain	13	10	77%	0	0	-	13	7	54%
060	Fernandez, Alvaro	Guatemala	26	26	100%	0	0	-	24	20	83%

(Modified Applicant's Tables 11 and 12, Volume 13 of 22, pages 86-89)

Appendix 7

Protocol 017
Applicant's Per Protocol Efficacy Analyses

Proportion of Patients With Favorable Clinical and Microbiological Response Assessments—
Microbiologically Evaluable Population
(Estimated)

Time Point	Treatment Group: MK-0826 1g (A) (N=203) n	Estimated† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) n	Estimated† Response %	(95% CI)	Estimated† Difference (A-B) %	(95% CI)
DCIV	203	92.1	(88.7, 95.5)	193	88.0	(83.7, 92.3)	4.1	(-2.2, 10.4)
EFU	202	89.1	(85.2, 93.0)	191	82.1	(76.9, 87.2)	7.0	(-0.3, 14.4)
TOC	203	86.7	(82.3, 91.1)	193	81.2	(76.0, 86.5)	5.5	(-2.2, 13.1)

† Computed from a statistical model adjusting for strata.
N = Number of microbiologically evaluable patients in each treatment group.
n = Number of microbiologically evaluable patients with assessments at the time point included in the analysis.
CI = Confidence interval.
DCIV= Discontinuation of intravenous therapy.
EFU = Early follow-up.
TOC = Test of cure.

(Applicant's Table 32, Volume 13 of 22, page 144)

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments At Test of Cure
Displayed by Site of Infection Stratum—
Microbiologically Evaluable Population
(Observed Data)

Site of Infection	Treatment Group: MK-0826 1 g (A) (N=203) n/m	Observed† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
Complicated Appendicitis‡	85/94	90.4	(84.4, 96.4)	82/91	90.1	(83.9, 96.3)	0.3
All Other Diagnoses	91/109	83.5	(76.5, 90.5)	75/102	73.5	(64.9, 82.1)	10.0
Overall	176/203	86.7	(82.0, 91.4)	157/193	81.3	(75.8, 86.9)	5.4

† Computed from a statistical model pooling across APACHE II score strata.
‡ Without generalized peritonitis.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

(Applicant's Table 33, Volume 13 of 22, page 146)

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments
At Test of Cure
Displayed by APACHE II Score Stratum—
Microbiologically Evaluable Population
(Observed Data)

APACHE II Score	Treatment Group: MK-0826 1 g (A) (N=203) n/m	Observed† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) Difference n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
≤15	169/192	88.0	(83.4, 92.6)	147/181	81.2	(75.5, 86.9)	6.8
>15	7/11	63.6	(33.8, 93.5)	10/12	83.3	(61.3, 100)	-19.7
Overall	176/203	86.7	(82.0, 91.4)	157/193	81.3	(75.8, 86.9)	5.4

† Computed from a statistical model pooling across diagnoses strata.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

(Applicant's Table 34, Volume 13 of 22, page 147)

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure
Displayed by Site of Infection and APACHE II Score Strata—
Microbiologically Evaluable Population
(Observed Data)

Stratum	Treatment Group: MK-0826 1 g (A) (N=203) n/m	Observed† Response % (95% CI)	Piperacillin/Tazobactam (B) (N=193) n/m	Observed† Response % (95% CI)	Observed Differences (A-B) %
Complicated Appendicitis‡, APACHE II score ≤15	83/92	90.2 (84.1, 96.3)	79/88	89.8 (83.4, 96.1)	0.4
Complicated Appendicitis‡, APACHE II score >15	2/2	100 --	3/3	100 --	0.0
All Other Diagnoses, APACHE II score ≤15	86/100	86.0 (79.2, 92.8)	68/93	73.1 (64.1, 82.2)	12.9
All Other Diagnoses, APACHE II score >15	5/9	55.6 --	7/9	77.8 --	-22.2
Overall	176/203	86.7 (82.0, 91.4)	157/193	81.3 (75.8, 86.9)	5.4

† For overall, computed from a statistical model pooling across strata.
‡ Without generalized peritonitis.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

(Applicant's Table 35, Volume 13 of 22, page 148)

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Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure
Displayed by Primary Site of Infection—
Microbiologically Evaluable Population
(Observed Data)

Primary Site of Infection†	MK-0826 1g (N=203) n/m (%)	Piperacillin/Tazobactam (N=193) n/m (%)
Stomach/Duodenum	9/10 (90.0)	7/9 (77.8)
Biliary-Cholecystitis	12/13 (92.3)	9/9 (100)
Biliary-Cholangitis	-	0/1 (0.0)
Small Bowel	11/12 (91.7)	7/9 (77.8)
Appendix	111/125 (88.8)	102/113 (90.3)
Colon	24/32 (75.0)	23/34 (67.6)
Parenchymal (liver)	0/1 (0.0)	1/2 (50.0)
Parenchymal (spleen)	-	0/1 (0.0)
Pelvic Inflammatory Disease	1/1 (100)	-
Other	8/9 (88.9)	8/15 (53.3)

† Only 1 site indicated per patient.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
- = No observation.

(Applicant's Table 36, Volume 13 of 22, page 150)

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Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure Displayed by Gender, Age Category, and Race— Microbiologically Evaluable Population (Observed Data)

	Treatment Group						Observed Difference (A-B) %
	MK-0826 1 g (A) (N=203)			Piperacillin/Tazobactam (B) (N=193)			
	n/m	Observed† Response % (95% CI)		n/m	Observed† Response % (95% CI)		
Gender							
Female	60/70	85.7	(77.5, 94.0)	48/62	77.4	(66.9, 87.9)	8.3
Male	116/133	87.2	(81.5, 92.9)	109/131	83.2	(76.8, 89.6)	4.0
Age Category							
<65	154/170	90.6	(85.2, 94.5)	129/162	79.6	(72.6, 85.5)	11.0
≥65	22/33	66.7	(48.2, 82.0)	28/31	90.3	(74.2, 98.0)	-23.7
<75	167/188	88.8	(83.4, 93.0)	146/182	80.2	(73.7, 85.7)	8.6
≥75	9/15	60.0	(32.3, 83.7)	11/11	100	(71.5, 100)	-40.0
Race							
African	1/1	100	-		-	-	-
Armenian	1/1	100	-		-	-	-
Asian	2/3	66.7	-	2/4	50.0	-	16.7
Black	5/5	100	-	4/6	66.7	-	33.3
Caucasian	90/107	84.1	(75.8, 90.5)	81/100	81.0	(71.9, 88.2)	3.1
Colored	1/1	100	-	1/1	100	-	0.0
Hispanic	66/72	91.7	(82.7, 96.9)	57/67	85.1	(74.3, 92.6)	6.6
Mestizo	2/3	66.7	-	2/2	100	-	-33.3
Mixed	8/10	80.0	(44.4, 97.5)	9/12	75.0	(42.8, 94.5)	5.0
Not specified	-	-	-	1/1	100	-	-

† Computed from a statistical model pooling across strata.

N = Number of microbiologically evaluable patients in each treatment group.

n/m = Number of patients with favorable assessment/number of patients with assessment.

CI = Confidence interval.

(Applicant's Table 41, Volume 13 of 22, page 156)

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure Displayed by Blinding Procedure— Microbiologically Evaluable Population (Observed Data)

Enhanced Blinding Procedure	Treatment Group: MK-0826 1 g (A) (N=203) n/m	Observed† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
No	112/131	85.5	(79.4, 91.5)	101/126	80.2	(73.2, 87.1)	5.3
Yes	64/72	88.9	(81.6, 96.2)	56/67	83.6	(74.6, 92.5)	5.3

† Computed from a statistical model pooling across strata.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

(Applicant's Table 42, Volume 13 of 22, page 157)

Proportion of Patients With Favorable Overall Microbiologic Response Assessments in the Microbiologically Evaluable Population (Estimated)

Time Point	Treatment Group: MK-0826 1 g (A) (N=203) n	Estimated† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) n	Estimated† Response %	(95% CI)	Estimated† Difference (A-B) %	(95% CI)
DCIV	203	93.6	(90.6, 96.6)	193	90.6	(86.7, 94.6)	3.0	(-2.8, 8.8)
EFU	202	89.6	(85.8, 93.4)	191	82.6	(77.5, 87.7)	7.0	(-0.3, 14.2)
TOC	203	89.1	(85.2, 93.1)	193	84.4	(79.5, 89.3)	4.8	(-2.4, 11.9)

† Computed from a statistical model adjusting for strata.
N = Number of microbiologically evaluable patients in each treatment group.
n = Number of microbiologically evaluable patients with assessment at each time point included in the analysis.
CI = Confidence interval.
DCIV = Discontinuation of intravenous therapy; EFU = Early follow-up; TOC = Test of cure.

(Applicant's Table 47, Volume 13 of 22, page 163)

Proportion of Favorable Microbiologic Response Assessments at Test of Cure
Displayed by Baseline Pathogen in the Microbiologically Evaluable Population—Total Isolates
(Observed Data)

Total Isolates	Treatment Group: MK-0826 1 g (A) (N=203) n/m	Observed[1] Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=193) n/m	Observed[1] Response %	(95% CI)	Observed Difference (A-B) %
Gram-Positive Aerobic Cocci	**117/131**	**89.3**	**(82.7, 94.0)**	**93/117**	**79.5**	**(71.0, 86.4)**	**9.8**
Enterococcus	15/17	88.2	(63.6, 98.5)	9/10	90.0	(55.5, 99.7)	-1.8
Enterococcus avium	10/11	90.9	(58.7, 99.8)	4/4	100	-	-9.1
Enterococcus casseliflavus	-	-	-	1/1	100	-	-
Enterococcus faecalis	23/25	92.0	(74.0, 99.0)	12/17	70.6	(44.0, 89.7)	21.4
Enterococcus faecium	6/7	85.7	-	1/4	25.0	-	60.7
Enterococcus gallinarum	1/1	100	-	0/1	0.0	-	100
Gemella morbillorum	1/1	100	-	-	-	-	-
Micrococcus	-	-	-	1/1	100	-	-
Staphylococcus	1/1	100	-	1/1	100	-	0.0
Staphylococcus aureus	4/5	80.0	-	3/3	100	-	-20.0
Staphylococcus epidermidis	4/4	100	-	3/4	75.0	-	25.0
Staphylococcus haemolyticus	3/3	100	-	-	-	-	-
Staphylococcus, coagulase negative	3/3	100	-	4/6	66.7	-	33.3
Streptococcus	5/6	83.3	-	7/8	87.5	-	-4.2
Streptococcus (alpha-hemolytic)	4/5	80.0	-	6/7	85.7	-	-5.7
Streptococcus (beta-hemolytic)	4/4	100	-	1/3	33.3	-	66.7
Streptococcus (Group C)	-	-	-	1/1	100	-	-
Streptococcus (Group D)	5/5	100	-	3/3	100	-	0.0
Streptococcus (Group F)	2/2	100	-	0/1	0.0	-	100
Streptococcus (microaerophilic)	0/1	0.0	-	-	-	-	-
Streptococcus (nonhemolytic)	0/1	0.0	-	-	-	-	-
Streptococcus agalactiae	1/1	100	-	1/2	50.0	-	50.0
Streptococcus anginosus	1/1	100	-	1/1	100	-	0.0
Streptococcus bovis	1/1	100	-	3/3	100	-	0.0
Streptococcus constellatus	1/1	100	-	3/4	75.0	-	25.0
Streptococcus intermedius	2/2	100	-	4/4	100	-	0.0
Streptococcus milleri group	5/5	100	-	4/6	66.7	-	33.3
Streptococcus mitis	1/1	100	-	-	-	-	-
Streptococcus pneumoniae	-	-	-	1/1	100	-	-
Streptococcus pyogenes	1/1	100	-	2/2	100	-	0.0
Streptococcus salivarius	2/2	100	-	-	-	-	-
Streptococcus sanguinis	1/1	100	-	-	-	-	-
Streptococcus viridans group	10/13	76.9	(46.2, 95.0)	15/17	88.2	(63.6, 98.5)	-11.3
Gram-Negative Aerobic Rods	**223/248**	**89.9**	**(85.5, 93.4)**	**199/233**	**85.4**	**(80.2, 89.7)**	**4.5**
Acinetobacter	-	-	-	2/2	100	-	-
Acinetobacter baumannii	2/2	100	-	-	-	-	-
Acinetobacter calcoaceticus	4/4	100	-	2/3	66.7	-	33.3
Acinetobacter lwoffi	1/1	100	-	2/2	100	-	0.0
Aeromonas hydrophila	1/1	100	-	-	-	-	-
Alcaligenes faecalis	1/1	100	-	-	-	-	-
Campylobacter gracilis	1/1	100	-	3/3	100	-	0.0
Citrobacter	-	-	-	1/1	100	-	-
Citrobacter amalonaticus	-	-	-	1/1	100	-	-
Citrobacter freundii	-	-	-	1/2	50.0	-	-
Citrobacter koseri	-	-	-	1/1	100	-	-
Comamonas testosteroni	-	-	-	0/1	0.0	-	-
Ekenella corrodens	-	-	-	1/1	100	-	-
Enterobacter	1/1	100	-	2/2	100	-	0.0
Enterobacter aerogenes	1/2	50.0	-	3/3	100	-	-50.0
Enterobacter cloacae	1/1	100	-	6/6	100	-	0.0
Enterobacter gergoviae	3/3	100	-	-	-	-	0.0
Enterobacter intermedius	1/1	100	-	1/1	100	-	-
Enterobacter sakazakii	-	-	-	-	-	-	-
Escherichia coli	1/1	100	-	1/1	100	-	-
Gram-negative aerobic rods	142/158	89.9	(84.1, 94.1)	114/135	84.4	(77.2, 90.1)	5.4
Haemophilus parainfluenzae	1/1	100	-	-	-	-	-
Hafnia alvei	-	-	-	1/2	50.0	-	-
Klebsiella	-	-	-	1/1	100	-	-
Klebsiella oxytoca	4/5	80.0	-	2/2	100	-	-
Klebsiella ozaenae	6/6	100	-	4/4	100	-	-20.0
Klebsiella pneumoniae	1/1	100	-	3/3	100	-	0.0
Morganella morganii	13/14	92.9	(66.1, 99.8)	12/17	70.6	(44.0, 89.7)	0.0
Pasteurella agglomerans	2/2	100	-	-	-	-	22.3
Proteus mirabilis	2/2	100	-	3/3	100	-	-
Proteus vulgaris	6/7	85.7	-	3/3	100	-	0.0
Pseudomonas	5/5	100	-	1/2	50.0	-	-14.3
Pseudomonas aeruginosa	-	-	-	1/1	100	-	50.0
Pseudomonas alcaligenes	21/26	80.8	(60.6, 93.4)	23/26	88.5	(69.8, 97.6)	-
Pseudomonas fluorescens	-	-	-	1/1	100	-	-7.7
Pseudomonas mendocina	-	-	-	1/1	100	-	-
Pseudomonas stutzeri	-	-	-	1/1	100	-	-
Serratia marcescens	-	-	-	1/1	100	-	-
Shewanella putrefaciens	-	-	-	1/1	100	-	-
Sphingomonas paucimobilis	1/1	100	-	-	-	-	-
	1/1	100	-	-	-	-	-