CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-337/S-021

Trade Name: INVANZÈ

Generic Name: Ertapenem sodium

Sponsor: Merck & Co., Inc.

Approval Date: August 10, 2006

Indications: for the prophylaxis of surgical site infection following elective colorectal surgery

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-337/S-021

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, MD
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your supplemental new drug application dated November 9, 2005, received November 10, 2005 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVANZ® (Ertapenem Sodium).

We acknowledge receipt of your submissions dated January 20, February 13, February 17, March 20, March 23, April 6, April 18, April 27, May 11 (2), June 1, June 19, and June 23, 2006.

This supplemental new drug application provides for the use of INVANZ® (Ertapenem Sodium) for the prophylaxis of surgical site infection following elective colorectal surgery.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-337/S-021**". Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susmita Samanta, MD, Regulatory Project Manager, at (301) 796-1400.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

8/10/2006 02:04:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

LABELING

INVANZ®
(ERTAPENEM FOR INJECTION)

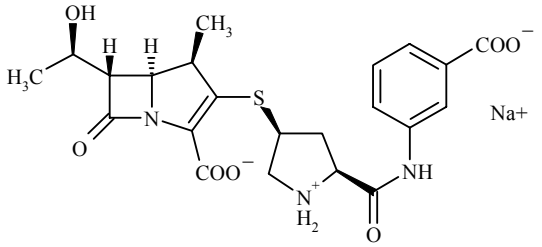
To reduce the development of drug-resistant bacteria and maintain the effectiveness of INVANZ and other antibacterial drugs, INVANZ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intravenous or Intramuscular Use

DESCRIPTION

INVANZ* (Ertapenem for Injection) is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics.

Chemically, INVANZ is described as [4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt. Its molecular weight is 497.50. The empirical formula is $C_{22}H_{24}N_3O_7SNa$, and its structural formula is:



Ertapenem sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

INVANZ is supplied as sterile lyophilized powder for intravenous infusion after reconstitution with appropriate diluent (see DOSAGE AND ADMINISTRATION, PREPARATION OF SOLUTION) and transfer to 50 mL 0.9% Sodium Chloride Injection or for intramuscular injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 grams ertapenem sodium, equivalent to 1 gram ertapenem. The sodium content is approximately 137 mg (approximately 6.0 mEq).

Each vial of INVANZ contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Average plasma concentrations (mcg/mL) of ertapenem following a single 30-minute infusion of a 1 g intravenous (IV) dose and administration of a single 1 g intramuscular (IM) dose in healthy young adults are presented in Table 1.

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* Registered trademark of MERCK & CO., Inc.

Table 1
Plasma Concentrations of Ertapenem in Adults After Single Dose Administration

	Average Plasma Concentrations (mcg/mL)								
Dose/Route	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
1 g IV*	155	115	83	48	31	20	9	3	1
1 g IM	33	53	67	57	40	27	13	4	2

*Infused at a constant rate over 30 minutes

The area under the plasma concentration-time curve (AUC) of ertapenem in adults increased less-than dose-proportional based on total ertapenem concentrations over the 0.5 to 2 g dose range, whereas the AUC increased greater-than dose proportional based on unbound ertapenem concentrations. Ertapenem exhibits non-linear pharmacokinetics due to concentration-dependent plasma protein binding at the proposed therapeutic dose. (See CLINICAL PHARMACOLOGY, *Distribution*.)

There is no accumulation of ertapenem following multiple IV or IM 1 g daily doses in healthy adults.

Average plasma concentrations (mcg/mL) of ertapenem in pediatric patients are presented in Table 2.

Table 2
Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration

Age Group	Dose	Average Plasma Concentrations (mcg/mL)							
		0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 to 23 months	15 mg/kg†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	-
		126.8	87.6	58.7	28.4	-	12.0	3.4	0.4
	20 mg/kg†	199.1	144.1	95.7	58.0	-	20.2	7.7	0.6
	40 mg/kg‡								
2 to 12 years	15 mg/kg†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	-
		147.6	97.6	63.2	34.5	-	12.3	4.9	0.5
	20 mg/kg†	241.7	152.7	96.3	55.6	-	18.8	7.2	0.6
	40 mg/kg‡								
13 to 17 years	20 mg/kg†	170.4	98.3	67.8	40.4	-	16.0	7.0	1.1
		155.9	110.9	74.8	-	24.0	-	6.2	-
	1 g§	255.0	188.7	127.9	76.2	-	31.0	15.3	2.1
	40 mg/kg‡								

* Infused at a constant rate over 30 minutes
† up to a maximum dose of 1 g/day
‡ up to a maximum dose of 2 g/day
§ Based on three patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies

Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without epinephrine), is almost completely absorbed following intramuscular (IM) administration at the recommended dose of 1 g. The mean bioavailability is approximately 90%. Following 1 g daily IM administration, mean peak plasma concentrations (C_{max}) are achieved in approximately 2.3 hours (T_{max}).

Distribution

Ertapenem is highly bound to human plasma proteins, primarily albumin. In healthy young adults, the protein binding of ertapenem decreases as plasma concentrations increase, from approximately

95% bound at an approximate plasma concentration of <100 micrograms (mcg)/mL to approximately 85% bound at an approximate plasma concentration of 300 mcg/mL.

The apparent volume of distribution at steady state (V_{ss}) of ertapenem in adults is approximately 0.12 liter/kg, approximately 0.2 liter/kg in pediatric patients 3 months to 12 years of age and approximately 0.16 liter/kg in pediatric patients 13 to 17 years of age.

The concentrations of ertapenem achieved in suction-induced skin blister fluid at each sampling point on the third day of 1 g once daily IV doses are presented in Table 3. The ratio of AUC_{0-24} in skin blister fluid/AUC_{0-24} in plasma is 0.61.

Table 3
Concentrations (mcg/mL) of Ertapenem in Adult Skin Blister Fluid at each Sampling Point on the Third Day of 1-g Once Daily IV Doses

0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

The concentration of ertapenem in breast milk from 5 lactating women with pelvic infections (5 to 14 days postpartum) was measured at random time points daily for 5 consecutive days following the last 1 g dose of intravenous therapy (3-10 days of therapy). The concentration of ertapenem in breast milk within 24 hours of the last dose of therapy in all 5 women ranged from <0.13 (lower limit of quantitation) to 0.38 mcg/mL; peak concentrations were not assessed. By day 5 after discontinuation of therapy, the level of ertapenem was undetectable in the breast milk of 4 women and below the lower limit of quantitation (<0.13 mcg/mL) in 1 woman.

Metabolism

In healthy young adults, after infusion of 1 g IV radiolabeled ertapenem, the plasma radioactivity consists predominantly (94%) of ertapenem. The major metabolite of ertapenem is the inactive ring-opened derivative formed by hydrolysis of the beta-lactam ring.

In vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. (See DRUG INTERACTIONS.)

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. (See PRECAUTIONS, *Drug Interactions*.)

Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.8 L/hour. The mean plasma half-life in pediatric patients 13 to 17 years of age is approximately 4 hours and approximately 2.5 hours in pediatric patients 3 months to 12 years of age.

Following the administration of 1 g IV radiolabeled ertapenem to healthy young adults, approximately 80% is recovered in urine and 10% in feces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged drug and approximately 37% as the ring-opened metabolite.

In healthy young adults given a 1 g IV dose, the mean percentage of the administered dose excreted in urine was 17.4% during 0-2 hours postdose, 5.4% during 4-6 hours postdose, and 2.4% during 12-24 hours postdose.

Special Populations

Renal Insufficiency

Total and unbound fractions of ertapenem pharmacokinetics were investigated in 26 adult subjects (31 to 80 years of age) with varying degrees of renal impairment. Following a single 1 g IV dose of ertapenem, the unbound AUC increased 1.5-fold and 2.3-fold in subjects with mild renal insufficiency (CL_{CR} 60-90 mL/min/1.73 m^2) and moderate renal insufficiency (CL_{CR} 31-59 mL/min/1.73 m^2), respectively, compared with healthy young subjects (25 to 45 years of age). No dosage adjustment is

necessary in patients with CL_{CR} ≥31 mL/min/1.73 m^2. The unbound AUC increased 4.4-fold and 7.6-fold in subjects with advanced renal insufficiency (CL_{CR} 5-30 mL/min/1.73 m^2) and end-stage renal insufficiency (CL_{CR} <10 mL/min/1.73 m^2), respectively, compared with healthy young subjects. The effects of renal insufficiency on AUC of total drug were of smaller magnitude. The recommended dose of ertapenem in adult patients with CL_{CR} ≤30 mL/min/1.73 m^2 is 0.5 grams every 24 hours. Following a single 1 g IV dose given immediately prior to a 4 hour hemodialysis session in 5 adult patients with end-stage renal insufficiency, approximately 30% of the dose was recovered in the dialysate. A supplementary dose of 150 mg is recommended if ertapenem is administered within 6 hours prior to hemodialysis. (See DOSAGE AND ADMINISTRATION.) There are no data in pediatric patients with renal insufficiency.

Hepatic Insufficiency

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. However, ertapenem does not appear to undergo hepatic metabolism based on *in vitro* studies and approximately 10% of an administered dose is recovered in the feces. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Gender

The effect of gender on the pharmacokinetics of ertapenem was evaluated in healthy male (n=8) and healthy female (n=8) subjects. The differences observed could be attributed to body size when body weight was taken into consideration. No dose adjustment is recommended based on gender.

Geriatric Patients

The impact of age on the pharmacokinetics of ertapenem was evaluated in healthy male (n=7) and healthy female (n=7) subjects ≥65 years of age. The total and unbound AUC increased 37% and 67%, respectively, in elderly adults relative to young adults. These changes were attributed to age-related changes in creatinine clearance. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

Pediatric Patients

Plasma concentrations of ertapenem are comparable in pediatric patients 13 to 17 years of age and adults following a 1 g once daily IV dose.

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age (N=6) were generally comparable to those in healthy young adults.

Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily IV dose in adults (see *Pharmacokinetics*). The plasma clearance (mL/min/kg) of ertapenem in patients 3 months to 12 years of age is approximately 2-fold higher as compared to that in adults. At the 15 mg/kg dose, the AUC value (doubled to model a twice daily dosing regimen, i.e., 30 mg/kg/day exposure) in patients 3 months to 12 years of age was comparable to the AUC value in young healthy adults receiving a 1 g IV dose of ertapenem.

Microbiology

Ertapenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta-lactamases.

Ertapenem has been shown to be active against most isolates of the following microorganisms *in vitro* and in clinical infections. (See INDICATIONS AND USAGE):

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus (methicillin susceptible isolates only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)

Streptococcus pyogenes

Note: Methicillin-resistant staphylococci and *Enterococcus* spp. are resistant to ertapenem.

Aerobic and facultative gram-negative microorganisms:

Escherichia coli
Haemophilus influenzae (Beta-lactamase negative isolates only)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

Anaerobic microorganisms:

Bacteroides fragilis
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Clostridium clostridioforme
Eubacterium lentum
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella bivia

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem; however, the safety and effectiveness of ertapenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

Aerobic and facultative gram-positive microorganisms:

Staphylococcus epidermidis (methicillin susceptible isolates only)
Streptococcus pneumoniae (penicillin-intermediate isolates only)

Aerobic and facultative gram-negative microorganisms:

Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae (Beta-lactamase positive isolates)
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic microorganisms:

Bacteroides vulgatus
Clostridium perfringens
Fusobacterium spp.

Susceptibility Test Methods:

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.

The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method[1,2] or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 4.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg ertapenem to test the susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria should be interpreted according to criteria provided in Table 4.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to ertapenem as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to criteria provided in Table 4.

Table 4
Susceptibility Interpretive Criteria for Ertapenem

Pathogen	Minimum Inhibitory Concentrations[a] MIC (µg/mL)			Disk Diffusion[a] Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae and *Staphylococcus* spp.	≤2.0	4.0	≥8.0	≥19	16-18	≤15
Haemophilus spp.	≤0.5	-	-	≥19	-	-
Streptococcus pneumoniae [b,c]	≤1.0	-	-	≥19	-	-
Streptococcus spp. other than *Streptococcus pneumoniae* [d,e]	≤1.0	-	-	≥19	-	-
Anaerobes	≤4.0	8.0	≥16.0	-	-	-

[a] The current absence of data in resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

[b] *Streptococcus pneumoniae* that are susceptible to penicillin (penicillin MIC ≤0.06 µg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[c] *Streptococcus pneumoniae* that are susceptible to penicillin (1-µg oxacillin disk zone diameter ≥20 mm), can be considered susceptible to ertapenem. Isolates with 1-µg oxacillin zone diameter ≤19 mm should be tested against ertapenem using an MIC method.

[d] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤0.12 µg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[e] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (10-units penicillin disk zone diameter ≥24 mm), can be considered susceptible to ertapenem. Isolates with 10-units penicillin disk zone diameter <24 mm should be tested against ertapenem using an MIC method. Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci and they should not be tested against ertapenem.

Note: *Staphylococcus* spp. can be considered susceptible to ertapenem if the penicillin MIC is ≤0.12 µg/mL. If the penicillin MIC is >0.12 µg/mL, then test oxacillin. *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin MIC is ≤2.0 µg/mL and resistant to ertapenem if the oxacillin MIC is ≥4.0 µg/mL. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin MIC is ≤0.25 µg/mL and resistant to ertapenem if the oxacillin MIC ≥0.5 µg/mL.

Staphylococcus spp. can be considered susceptible to ertapenem if the penicillin (10 U disk) zone is ≥29 mm. If the penicillin zone is ≤28 mm, then test oxacillin by disk diffusion (1 µg disk). *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin (1 µg disk) zone is ≥13 mm and resistant to ertapenem if the oxacillin zone is ≤10 mm. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin zone is ≥18 mm and resistant to ertapenem if the oxacillin (1 µg disk) zone is ≤17 mm.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures[1,2,3,4]. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant. Standard ertapenem powder should provide the following range of values noted in Table 5.

Table 5
Acceptable Quality Control Ranges for Ertapenem

Microorganism	Minimum Inhibitory Concentrations MIC Range (µg/mL)	Disk Diffusion Zone Diameter (mm)
Escherichia coli ATCC 25922	0.004-0.016	29-36
Haemophilus influenzae ATCC 49766	0.016-0.06	27-33
Staphylococcus aureus ATCC 29213	0.06-0.25	-
Staphylococcus aureus ATCC 25923	-	24-31
Streptococcus pneumoniae ATCC 49619	0.03-0.25	28-35
	0.06-0.5[f]	-
Bacteroides fragilis ATCC 25285	0.06-0.25[g]	
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0[f]	-
	0.25-1.0[g]	
Eubacterium lentum ATCC 43055	0.5-4.0[f]	-
	0.5-2.0[g]	

[f] Quality control ranges for broth microdilution testing
[g] Quality control ranges for agar microdilution testing

INDICATIONS AND USAGE

Treatment

INVANZ is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible isolates of the designated microorganisms. (See DOSAGE AND ADMINISTRATION):

Complicated Intra-abdominal Infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, or *Bacteroides uniformis*.

Complicated Skin and Skin Structure Infections, including diabetic foot infections without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*. INVANZ has not been studied in diabetic foot infections with concomitant osteomyelitis (see CLINICAL STUDIES).

Community Acquired Pneumonia due to *Streptococcus pneumoniae* (penicillin susceptible isolates only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates only), or *Moraxella catarrhalis*.

Complicated Urinary Tract Infections including pyelonephritis due to *Escherichia coli*, including cases with concurrent bacteremia, or *Klebsiella pneumoniae*.

Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections due to *Streptococcus agalactiae, Escherichia coli*, *Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia*.

Prevention

INVANZ is indicated in adults for the **prophylaxis of surgical site infection following elective colorectal surgery**.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ertapenem. Therapy with INVANZ (ertapenem) may be initiated empirically before results of these tests are known; once results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of INVANZ and other antibacterial drugs, INVANZ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

INVANZ is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

Due to the use of lidocaine HCl as a diluent, INVANZ administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type. (Refer to the prescribing information for lidocaine HCl.)

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH INVANZ, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO INVANZ OCCURS, DISCONTINUE THE DRUG

IMMEDIATELY. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.**

Seizures and other CNS adverse experiences have been reported during treatment with INVANZ. (See PRECAUTIONS and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Lidocaine HCl is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine HCl.

PRECAUTIONS

General

During clinical investigations in adult patients treated with INVANZ (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14-day follow-up period. (See ADVERSE REACTIONS.) These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal

function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of INVANZ re-examined to determine whether it should be decreased or the antibiotic discontinued. Dosage adjustment of INVANZ is recommended in patients with reduced renal function. (See DOSAGE AND ADMINISTRATION.)

As with other antibiotics, prolonged use of INVANZ may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing INVANZ in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Caution should be taken when administering INVANZ intramuscularly to avoid inadvertent injection into a blood vessel. (See DOSAGE AND ADMINISTRATION.)

Lidocaine HCl is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine HCl for additional precautions.

Information for patients

Patients should be counseled that antibacterial drugs including INVANZ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When INVANZ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment

and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by INVANZ or other antibacterial drugs in the future.

Laboratory Tests

While INVANZ possesses toxicity similar to the beta-lactam group of antibiotics, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions

When ertapenem is co-administered with probenecid (500 mg p.o. every 6 hours), probenecid competes for active tubular secretion and reduces the renal clearance of ertapenem. Based on total ertapenem concentrations, probenecid increased the AUC by 25% and reduced the plasma and renal clearances by 20% and 35%, respectively. The half-life increased from 4.0 to 4.8 hours. Because of the small effect on half-life, the coadministration with probenecid to extend the half-life of ertapenem is not recommended.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. *In vitro* studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following six cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance with the listed isoforms are unlikely. (See CLINICAL PHARMACOLOGY, *Distribution* and *Metabolism*.)

Other than with probenecid, no specific clinical drug interaction studies have been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ertapenem.

Ertapenem was neither mutagenic nor genotoxic in the following *in vitro* assays: alkaline elution/rat hepatocyte assay, chromosomal aberration assay in Chinese hamster ovary cells, and TK6 human lymphoblastoid cell mutagenesis assay; and in the *in vivo* mouse micronucleus assay.

In mice and rats, IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs) resulted in no effects on mating performance, fecundity, fertility, or embryonic survival.

Pregnancy: Teratogenic Effects

Pregnancy Category B: In mice and rats given IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs), there was no evidence of developmental toxicity as assessed by external, visceral, and skeletal examination of the fetuses. However, in mice given 700 mg/kg/day, slight decreases in average fetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae were observed. Ertapenem crosses the placental barrier in rats.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Ertapenem is excreted in human breast milk. (See CLINICAL PHARMACOLOGY, *Distribution*.) Caution should be exercised when INVANZ is administered to a nursing woman. INVANZ should be administered to nursing mothers only when the expected benefit outweighs the risk.

Labor and delivery

INVANZ has not been studied for use during labor and delivery.

Pediatric Use

Safety and effectiveness of INVANZ in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric

patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age with the following infections (see INDICATIONS AND USAGE and CLINICAL STUDIES):

- Complicated Intra-abdominal Infections
- Complicated Skin and Skin Structure Infections
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections
- Acute Pelvic Infections

INVANZ is not recommended in infants under 3 months of age as no data are available.

INVANZ is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration.

Geriatric Use

Of the 1,835 patients in Phase IIb/III studies treated with INVANZ, approximately 26 percent were 65 and over, while approximately 12 percent were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Of the total number of patients in clinical studies, 37 patients receiving ertapenem 1 g daily and 36 patients receiving comparator drugs were considered to have Child-Pugh Class A, B, or C liver impairment. The incidence of adverse experiences in patients with hepatic impairment was similar between the ertapenem group and the comparator groups.

ANIMAL PHARMACOLOGY

In repeat-dose studies in rats, treatment-related neutropenia occurred at every dose-level tested, including the lowest dose of 2 mg/kg (approximately 2% of the human dose on a body surface area basis).

Studies in rabbits and Rhesus monkeys were inconclusive with regard to the effect on neutrophil counts.

ADVERSE REACTIONS

Adults

Clinical studies enrolled 1954 patients treated with ertapenem; in some of the clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. (See CLINICAL STUDIES.) Most adverse experiences reported in these clinical studies were described as mild to moderate in severity. Ertapenem was discontinued due to adverse experiences in 4.7% of patients. Table 6 shows the incidence of adverse experiences reported in ≥1.0% of patients in these studies. The most common drug-related adverse experiences in patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea (5.5%), infused vein complication (3.7%), nausea (3.1%), headache (2.2%), vaginitis in females (2.1%), phlebitis/thrombophlebitis (1.3%), and vomiting (1.1%).

Table 6
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Adult Patients Treated With INVANZ in Clinical Studies

Adverse Events	INVANZ* 1 g daily (N=802)	Piperacillin/ Tazobactam * 3.375 g q6h (N=774)	INVANZ† 1 g daily (N=1152)	Ceftriaxone† 1 or 2 g daily (N=942)
Local:				
Extravasation	1.9	1.7	0.7	1.1
Infused vein complication	7.1	7.9	5.4	6.7
Phlebitis/thrombophlebitis	1.9	2.7	1.6	2.0
Systemic:				
Asthenia/fatigue	1.2	0.9	1.2	1.1
Death	2.5	1.6	1.3	1.6
Edema/swelling	3.4	2.5	2.9	3.3
Fever	5.0	6.6	2.3	3.4
Abdominal pain	3.6	4.8	4.3	3.9
Chest pain	1.5	1.4	1.0	2.5
Hypertension	1.6	1.4	0.7	1.0
Hypotension	2.0	1.4	1.0	1.2
Tachycardia	1.6	1.3	1.3	0.7
Acid regurgitation	1.6	0.9	1.1	0.6
Oral candidiasis	0.1	1.3	1.4	1.9
Constipation	4.0	5.4	3.3	3.1
Diarrhea	10.3	12.1	9.2	9.8
Dyspepsia	1.1	0.6	1.0	1.6
Nausea	8.5	8.7	6.4	7.4
Vomiting	3.7	5.3	4.0	4.0
Leg pain	1.1	0.5	0.4	0.3
Anxiety	1.4	1.3	0.8	1.2
Altered mental status‡	**5.1**	**3.4**	**3.3**	**2.5**
Dizziness	2.1	3.0	1.5	2.1
Headache	5.6	5.4	6.8	6.9
Insomnia	3.2	5.2	3.0	4.1
Cough	1.6	1.7	1.3	0.5
Dyspnea	2.6	1.8	1.0	2.4
Pharyngitis	0.7	1.4	1.1	0.6
Rales/rhonchi	1.1	1.0	0.5	1.0
Respiratory distress	1.0	0.4	0.2	0.2
Erythema	1.6	1.7	1.2	1.2
Pruritus	2.0	2.6	1.0	1.9
Rash	2.5	3.1	2.3	1.5
Vaginitis	1.4	1.0	3.3	3.7

* Includes Phase IIb/III Complicated intra-abdominal infections, Complicated skin and skin structure infections and Acute pelvic infections studies
† Includes Phase IIb/III Community acquired pneumonia and Complicated urinary tract infections, and Phase IIa studies
‡ Includes agitation, confusion, disorientation, decreased mental acuity, changed mental status, somnolence, stupor

In patients treated for complicated intra-abdominal infections, death occurred in 4.7% (15/316) of patients receiving ertapenem and 2.6% (8/307) of patients receiving comparator drug. These deaths occurred in patients with significant co-morbidity and/or severe baseline infections. Deaths were considered unrelated to study drugs by investigators.

In clinical studies, seizure was reported during study therapy plus 14-day follow-up period in 0.5% of patients treated with ertapenem, 0.3% of patients treated with piperacillin/tazobactam and 0% of patients treated with ceftriaxone. (See PRECAUTIONS.)

Additional adverse experiences that were reported with INVANZ with an incidence >0.1% within each body system are listed below:

Body as a whole: abdominal distention, pain, chills, septicemia, septic shock, dehydration, gout, malaise, necrosis, candidiasis, weight loss, facial edema, injection site induration, injection site pain, flank pain, and syncope;

Cardiovascular System: heart failure, hematoma, cardiac arrest, bradycardia, arrhythmia, atrial fibrillation, heart murmur, ventricular tachycardia, asystole, and subdural hemorrhage;

Digestive System: gastrointestinal hemorrhage, anorexia, flatulence, *C. difficile* associated diarrhea, stomatitis, dysphagia, hemorrhoids, ileus, cholelithiasis, duodenitis, esophagitis, gastritis, jaundice, mouth ulcer, pancreatitis, and pyloric stenosis;

Nervous System & Psychiatric: nervousness, seizure (see WARNINGS and PRECAUTIONS), tremor, depression, hypesthesia, spasm, paresthesia, aggressive behavior, and vertigo;

Respiratory System: pleural effusion, hypoxemia, bronchoconstriction, pharyngeal discomfort, epistaxis, pleuritic pain, asthma, hemoptysis, hiccups, and voice disturbance;

Skin & Skin Appendage: sweating, dermatitis, desquamation, flushing, and urticaria;

Special Senses: taste perversion;

Urogenital System: renal insufficiency, oliguria/anuria, vaginal pruritus, hematuria, urinary retention, bladder dysfunction, vaginal candidiasis, and vulvovaginitis.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the adverse experience profile was generally similar to that seen in previous clinical trials.

In a clinical study in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of ertapenem 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall adverse experience profile was generally comparable to that observed for ertapenem in previous clinical trials. Table 7 shows the incidence of adverse experiences other than those previously described above for ertapenem, regardless of causality, reported in ≥1.0% of patients in this study.

Table 7
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Adult Patients Treated With INVANZ for Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Adverse Events	INVANZ 1 g (N= 476)	Cefotetan 2 g (N= 476)
Anemia	5.7	6.9
Small intestinal obstruction	2.1	1.9
Cellulitis	1.5	1.5
C. difficile infection or colitis	1.7	0.6
Pneumonia	2.1	4.0
Postoperative infection	2.3	4.0
Urinary tract infection	3.8	5.5
Wound infection	6.5	12.4
Anastomotic leak	1.5	1.3
Seroma	1.3	1.9

Wound complication	2.9	2.3
Wound dehiscence	1.3	1.5
Wound secretion	1.9	2.1
Dysuria	1.1	1.3
Atelectasis	3.4	1.9

Additional adverse experiences that were reported in this prophylaxis study with INVANZ, regardless of causality, with an incidence <1.0% and >0.5% within each body system are listed below:

Gastrointestinal Disorders: dry mouth, hematochezia;

General Disorders and Administration Site Condition: crepitations;

Infections and Infestations: abdominal abscess, fungal rash, pelvic abscess;

Injury, Poisoning and Procedural Complications: incision site complication, incision site hemorrhage, intestinal stoma complication;

Musculoskeletal and Connective Tissue Disorders: muscle spasms;

Nervous System Disorders: cerebrovascular accident;

Renal and Urinary Disorders: pollakiuria;

Respiratory, Thoracic and Mediastinal Disorders: crackles lung, lung infiltration, pulmonary congestion, pulmonary embolism, wheezing.

Pediatric Patients

Clinical studies enrolled 384 patients treated with ertapenem; in some of the clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. (See CLINICAL STUDIES.) The overall adverse experience profile in pediatric patients is comparable to that in adult patients. Table 8 shows the incidence of adverse experiences reported in ≥1.0% of pediatric patients in clinical studies. The most common drug-related adverse experiences in pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea (6.5%), infusion site pain (5.5%), infusion site erythema (2.6%), vomiting (2.1%).

Table 8
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Pediatric Patients Treated With INVANZ in Clinical Studies

Adverse Events	INVANZ*† (N=384)	Ceftriaxone* (N=100)	Ticarcillin/ Clavulanate† (N=24)
Local:			
Infusion Site Erythema	3.9	3.0	8.3
Infusion Site Induration	1.0	1.0	0.0
Infusion Site Pain	7.0	4.0	20.8
Infusion Site Phlebitis	1.8	3.0	0.0
Infusion Site Swelling	1.8	1.0	4.2
Infusion Site Warmth	1.3	1.0	4.2
Systemic:			
Abdominal Pain	4.7	3.0	4.2
Upper Abdominal Pain	1.0	2.0	0.0
Constipation	2.3	0.0	0.0
Diarrhea	11.7	17.0	4.2
Loose Stools	2.1	0.0	0.0
Nausea	1.6	0.0	0.0
Vomiting	10.2	11.0	8.3
Pyrexia	4.9	6.0	8.3
Abdominal Abscess	1.0	0.0	4.2
Herpes Simplex	1.0	1.0	4.2
Nasopharyngitis	1.6	6.0	0.0
Upper Respiratory Tract Infection	2.3	3.0	0.0
Viral Pharyngitis	1.0	0.0	0.0

Hypothermia	1.6	1.0	0.0
Dizziness	1.6	0.0	0.0
Headache	4.4	4.0	0.0
Cough	4.4	3.0	0.0
Wheezing	1.0	0.0	0.0
Dermatitis	1.0	1.0	0.0
Pruritus	1.6	0.0	0.0
Diaper Dermatitis	4.7	4.0	0.0
Rash	2.9	2.0	8.3

* Includes Phase IIb Complicated skin and skin structure infections, Community acquired pneumonia and Complicated urinary tract infections studies in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g or ceftriaxone 50 mg/kg/day IV in two divided doses up to a maximum of 2 g, and patients 13 to 17 years of age received INVANZ 1 g IV daily or ceftriaxone 50 mg/kg/day IV in a single daily dose.

† Includes Phase IIb Acute pelvic infections and Complicated intra-abdominal infections studies in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g and patients 13 to 17 years of age received INVANZ 1 g IV daily or ticarcillin/clavulanate 50 mg/kg for patients <60 kg or ticarcillin/clavulanate 3.0 g for patients >60 kg, 4 or 6 times a day.

Additional adverse experiences that were reported with INVANZ with an incidence <1.0% and >0.5% within each body system are listed below:

General Disorders and Administration Site Condition: chest pain, infusion site pruritus;
Infections and Infestations: candidiasis, ear infection, oral candidiasis;
Metabolism and Nutrition Disorders: decreased appetite;
Musculoskeletal and Connective Tissue Disorders: arthralgia;
Nervous System Disorders: somnolence;
Psychiatric Disorders: insomnia;
Reproductive System and Breast Disorders: genital rash;
Respiratory, Thoracic and Mediastinal Disorders: pleural effusion, rhinitis, rhinorrhea;
Skin and Subcutaneous Tissue Disorders: dermatitis atopic, rash erythematous, skin lesion;
Vascular Disorders: *phlebitis.*

Post-Marketing Experience:

The following post-marketing adverse experiences have been reported:
Immune System: anaphylaxis including anaphylactoid reactions
Nervous System & Psychiatric: hallucinations

Adverse Laboratory Changes

Adults

Laboratory adverse experiences that were reported during therapy in ≥1.0% of adult patients treated with INVANZ in clinical studies are presented in Table 9. Drug-related laboratory adverse experiences that were reported during therapy in ≥1.0% of adult patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical studies were ALT increased (6.0%), AST increased (5.2%), serum alkaline phosphatase increased (3.4%), platelet count increased (2.8%), and eosinophils increased (1.1%). Ertapenem was discontinued due to laboratory adverse experiences in 0.3% of patients.

Table 9
Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up
in ≥1.0% of Adult Patients Treated With INVANZ in Clinical Studies

Adverse laboratory experiences	INVANZ‡ 1 g daily (n†=766)	Piperacillin / Tazobactam‡ 3.375 g q6h (n†=755)	INVANZ§ 1 g daily (n†=1122)	Ceftriaxone§ 1 or 2 g daily (n†=920)
ALT increased	8.8	7.3	8.3	6.9
AST increased	8.4	8.3	7.1	6.5
Serum albumin decreased	1.7	1.5	0.9	1.6
Serum alkaline phosphatase increased	6.6	7.2	4.3	2.8
Serum creatinine increased	1.1	2.7	0.9	1.2
Serum glucose increased	1.2	2.3	1.7	2.0
Serum potassium decreased	1.7	2.8	1.8	2.4
Serum potassium increased	1.3	0.5	0.5	0.7
Total serum bilirubin increased	1.7	1.4	0.6	1.1
Eosinophils increased	1.1	1.1	2.1	1.8
Hematocrit decreased	3.0	2.9	3.4	2.4
Hemoglobin decreased	4.9	4.7	4.5	3.5
Platelet count decreased	1.1	1.2	1.1	1.0
Platelet count increased	6.5	6.3	4.3	3.5
Segmented neutrophils decreased	1.0	0.3	1.5	0.8
Prothrombin time increased	1.2	2.0	0.3	0.9
WBC decreased	0.8	0.7	1.5	1.4
Urine RBCs increased	2.5	2.9	1.1	1.0
Urine WBCs increased	2.5	3.2	1.6	1.1

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test
† Number of patients with one or more laboratory tests
‡ Includes Phase IIb/III Complicated intra-abdominal infections, Complicated skin and skin structure infections and Acute pelvic infections studies
§ Includes Phase IIb/III Community acquired pneumonia and Complicated urinary tract infections, and Phase IIa studies

Additional laboratory adverse experiences that were reported during therapy in >0.1% but <1.0% of patients treated with INVANZ in clinical studies include: increases in BUN, direct and indirect serum bilirubin, serum sodium, monocytes, PTT, urine epithelial cells; decreases in serum bicarbonate.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the laboratory adverse experience profile was generally similar to that seen in previous clinical trials.

In a clinical study in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of ertapenem 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall laboratory adverse experience profile was generally comparable to that observed for ertapenem in previous clinical trials. Additional laboratory adverse experiences that were reported during therapy and the 14 days post surgery period in >1.0% of patients, regardless of causality, include: white blood cell count increased and urine protein present.

Pediatric Patients

Laboratory adverse experiences that were reported during therapy in ≥1.0% of pediatric patients treated with INVANZ in clinical studies are presented in Table 10. Drug-related laboratory adverse experiences that were reported during therapy in ≥2.0% of pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical studies were neutrophil count decreased (3.0%), ALT increased (2.2%), and AST increased (2.1%).

Table 10
Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Pediatric Patients Treated With INVANZ in Clinical Studies

Adverse laboratory experiences	INVANZ ($n^{\dagger}$=379)	Ceftriaxone ($n^{\dagger}$=97)	Ticarcillin / Clavulanate ($n^{\dagger}$=24)
ALT Increased	3.8	1.1	4.3
Alkaline Phosphatase Increased	1.1	0.0	0.0
AST Increased	3.8	1.1	4.3
Eosinophil Count Increased	1.1	2.1	0.0
Neutrophil Count Decreased	5.8	3.1	0.0
Platelet Count Increased	1.3	0.0	8.7

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at least 300 patients had the test
† Number of patients with one or more laboratory tests

Additional laboratory adverse experiences that were reported during therapy in >0.5% but <1.0% of patients treated with INVANZ in clinical studies include: white blood cell count decreased and urine protein present.

OVERDOSAGE

No specific information is available on the treatment of overdosage with INVANZ. Intentional overdosing of INVANZ is unlikely. Intravenous administration of INVANZ at a dose of 2 g over 30 min or 3 g over 1-2h in healthy adult volunteers resulted in an increased incidence of nausea. In clinical studies in adults, inadvertent administration of three 1 g doses of INVANZ in a 24 hour period resulted in diarrhea and transient dizziness in one patient. In pediatric clinical studies, a single IV dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

In the event of an overdose, INVANZ should be discontinued and general supportive treatment given until renal elimination takes place.

INVANZ can be removed by hemodialysis; the plasma clearance of the total fraction of ertapenem was increased 30% in subjects with end-stage renal insufficiency when hemodialysis (4 hour session) was performed immediately following administration. However, no information is available on the use of hemodialysis to treat overdosage.

DOSAGE AND ADMINISTRATION

The dose of INVANZ in patients 13 years of age and older is 1 gram (g) given once a day. The dose of INVANZ in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day). INVANZ may be administered by intravenous infusion for up to 14 days or intramuscular injection for

up to 7 days. When administered intravenously, INVANZ should be infused over a period of 30 minutes.

Intramuscular administration of INVANZ may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

Table 11 presents treatment guidelines for INVANZ.

Table 11
Treatment Guidelines for Adults and Pediatric Patients With Normal Renal Function* and Body Weight

Infection†	Daily Dose (IV or IM) Adults and Pediatric Patients 13 years of age and older	Daily Dose (IV or IM) Pediatric Patients 3 months to 12 years of age	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	15 mg/kg twice daily§	5 to 14 days
Complicated skin and skin structure infections, including diabetic foot infections¶	1 g	15 mg/kg twice daily§	7 to 14 days‖
Community acquired pneumonia	1 g	15 mg/kg twice daily§	10 to 14 days‡
Complicated urinary tract infections, including pyelonephritis	1 g	15 mg/kg twice daily§	10 to 14 days‡
Acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections	1 g	15 mg/kg twice daily§	3 to 10 days

* defined as creatinine clearance >90 mL/min/1.73 m^2
† due to the designated pathogens (see INDICATIONS AND USAGE)
¶ INVANZ has not been studied in diabetic foot infections with concomitant osteomyelitis (see CLINICAL STUDIES).
‖ adult patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral switch therapy)
‡ duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.
§ not to exceed 1 g/day

Table 12 presents prophylaxis guidelines for INVANZ.

Table 12
Prophylaxis Guidelines for Adults

Indication	Daily Dose (IV) Adults	Recommended Duration of Total Antimicrobial Treatment
Prophylaxis of surgical site infection following elective colorectal surgery	1 g	Single intravenous dose given 1 hour prior to surgical incision

Patients with Renal Insufficiency: INVANZ may be used for the treatment of infections in adult patients with renal insufficiency. In patients whose creatinine clearance is >30 mL/min/1.73 m^2, no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m^2) and end-stage renal insufficiency (creatinine clearance ≤10 mL/min/1.73 m^2) should receive 500 mg daily. There are no data in pediatric patients with renal insufficiency.

Patients on Hemodialysis: When adult patients on hemodialysis are given the recommended daily dose of 500 mg of INVANZ within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session. If INVANZ is given at least 6 hours prior to hemodialysis, no supplementary dose is needed. There are no data in patients undergoing peritoneal dialysis or hemofiltration. There are no data in pediatric patients on hemodialysis.

When only the serum creatinine is available, the following formula** may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{(weight in kg) x (140-age in years)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females: (0.85) x (value calculated for males)

Patients with Hepatic Insufficiency: No dose adjustment recommendations can be made in patients with impaired hepatic function. (See CLINICAL PHARMACOLOGY, *Special Populations*, *Hepatic Insufficiency* and PRECAUTIONS.)

No dosage adjustment is recommended based on age (13 years of age and older) or gender. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

PREPARATION OF SOLUTION

Adults and pediatric patients 13 years of age and older

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection.

** Cockcroft and Gault equation: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976

3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:
INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% lidocaine HCl injection*** (**without epinephrine**). Shake vial thoroughly to form solution.
2. Immediately withdraw the contents of the vial and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY**.

Pediatric patients 3 months to 12 years of age:
Preparation for intravenous administration:
DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:
INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% lidocaine HCl injection*** (**without epinephrine**). Shake vial thoroughly to form solution.
2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY**.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. Solutions of INVANZ range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

STORAGE AND STABILITY

Before reconstitution

Do not store lyophilized powder above 25°C (77°F).

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see DOSAGE AND ADMINISTRATION, PREPARATION OF SOLUTION), **may be stored at room temperature (25°C) and used within 6 hours or stored for 24 hours under refrigeration (5°C) and used within 4 hours after removal from refrigeration. Solutions of INVANZ should not be frozen**.

*** Refer to the prescribing information for lidocaine HCl.

HOW SUPPLIED

INVANZ is supplied as a sterile lyophilized powder in single dose vials containing ertapenem for intravenous infusion or for intramuscular injection as follows:

No. 3843—1 g ertapenem equivalent
NDC 0006-3843-71 in trays of 10 vials
No. 3843—1 g ertapenem equivalent
NDC 0006-3843-45 in trays of 25 vials.

CLINICAL STUDIES

Adults

Complicated Intra-Abdominal Infections

Ertapenem was evaluated in adults for the treatment of complicated intra-abdominal infections in a clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 5 to 14 days and enrolled 665 patients with localized complicated appendicitis, and any other complicated intra-abdominal infection including colonic, small intestinal, and biliary infections and generalized peritonitis. The combined clinical and microbiologic success rates in the microbiologically evaluable population at 4 to 6 weeks posttherapy (test of cure) were 83.6% (163/195) for ertapenem and 80.4% (152/189) for piperacillin/tazobactam.

Complicated Skin and Skin Structure Infections

Ertapenem was evaluated in adults for the treatment of complicated skin and skin structure infections in a clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 7 to 14 days and enrolled 540 patients including patients with deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage. The clinical success rates at 10 to 21 days posttherapy (test of cure) were 83.9% (141/168) for ertapenem and 85.3% (145/170) for piperacillin/tazobactam.

Diabetic Foot Infections

Ertapenem was evaluated in adults for the treatment of diabetic foot infections without concomitant osteomyelitis in a multicenter, randomized, double-blind clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours). Test-of-cure was defined as clinical response between treatment groups in the clinically evaluable population at the 10-day posttherapy follow-up visit. The study included 295 patients randomized to ertapenem and 291 patients to piperacillin/tazobactam. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 5 to 28 days of treatment (parenteral and oral). All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement, as is typically required in the treatment of diabetic foot infections, and most patients received these treatments. Patients with suspected osteomyelitis could be enrolled if all the infected bone was removed within 2 days of initiation of study therapy, and preferably within the prestudy period. Investigators had the option to add open-label vancomycin if enterococci or methicillin-resistant *Staphylococcus aureus* (MRSA) were among the pathogens isolated or if patients had a history of MRSA infection and additional therapy was indicated in the opinion of the investigator. Two hundred and four (204) patients randomized to ertapenem and 202 patients randomized to piperacillin/tazobactam were clinically evaluable. The clinical success rates at 10 days posttherapy were 75.0% (153/204) for ertapenem and 70.8% (143/202) for piperacillin/tazobactam.

Community Acquired Pneumonia

Ertapenem was evaluated in adults for the treatment of community acquired pneumonia in two clinical trials. Both studies compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 866 patients. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 10 to 14 days of treatment (parenteral and oral). In the first study the primary efficacy parameter was the clinical success rate in the clinically evaluable population and success rates were 92.3% (168/182) for ertapenem and 91.0% (183/201) for ceftriaxone

at 7 to 14 days posttherapy (test of cure). In the second study the primary efficacy parameter was the clinical success rate in the microbiologically evaluable population and success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone at 7 to 14 days posttherapy (test of cure).

Complicated Urinary Tract Infections Including Pyelonephritis

Ertapenem was evaluated in adults for the treatment of complicated urinary tract infections including pyelonephritis in two clinical trials. Both studies compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 850 patients. Both regimens allowed the option to switch to oral ciprofloxacin (500 mg twice daily) for a total of 10 to 14 days of treatment (parenteral and oral). The microbiological success rates (combined studies) at 5 to 9 days posttherapy (test of cure) were 89.5% (229/256) for ertapenem and 91.1% (204/224) for ceftriaxone.

Acute Pelvic Infections Including Endomyometritis, Septic Abortion And Post-Surgical Gynecological Infections

Ertapenem was evaluated in adults for the treatment of acute pelvic infections in a clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 3 to 10 days and enrolled 412 patients including 350 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates in the clinically evaluable population at 2 to 4 weeks posttherapy (test of cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam.

Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Ertapenem was evaluated in adults for prophylaxis of surgical site infection following elective colorectal surgery in a multicenter, randomized, double-blind clinical trial. This study compared a single intravenous dose of ertapenem (1 g) versus cefotetan (2 g) administered over 30 minutes, 1 hour before elective colorectal surgery. Test-of-prophylaxis was defined as no evidence of surgical site infection, post-operative anastomotic leak, or unexplained antibiotic use in the clinically evaluable population up to and including at the 4-week posttreatment follow-up visit. The study included 500 patients randomized to ertapenem and 502 patients randomized to cefotetan. The modified intent-to-treat (MITT) population consisted of 451 ertapenem patients and 450 cefotetan patients and included all patients who were randomized, treated, and underwent elective colorectal surgery with adequate bowel preparation. The clinically evaluable population was a subset of the MITT population and consisted of patients who received a complete dose of study therapy no more than two hours prior to surgical incision and no more than six hours before surgical closure. Clinically evaluable patients had sufficient information to determine outcome at the 4-week follow-up assessment and had no confounding factors that interfered with the assessment of that outcome. Examples of confounding factors included prior or concomitant antibiotic violations, the need for a second surgical procedure during the study period, and identification of a distant site infection with concomitant antibiotic administration and no evidence of subsequent wound infection. Three-hundred forty-six (346) patients randomized to ertapenem and 339 patients randomized to cefotetan were clinically evaluable. The prophylactic success rates at 4 weeks posttreatment in the clinically evaluable population were 70.5% (244/346) for ertapenem and 57.2% (194/339) for cefotetan (difference 13.3%, [95% CI: 6.1, 20.4], $p<0.001$). Prophylaxis failure due to surgical site infections occurred in 18.2% (63/346) (ertapenem patients and 31.0%(105/339) cefotetan patients. Post-operative anastomotic leak occurred in 2.9% (10/346) ertapenem patients and 4.1% (14/339) cefotetan patients. Unexplained antibiotic use occurred in 8.4% (29/346) ertapenem patients and 7.7% (26/339) cefotetan patients. Though patient numbers were small in some subgroups, in general, clinical response rates by age, gender, and race were consistent with the results found in the clinically evaluable population. In the MITT analysis, the prophylactic success rates at 4 weeks posttreatment were 58.3% (263/451) for ertapenem and 48.9% (220/450) for cefotetan (difference 9.4%, [95% CI: 2.9, 15.9], $p=0.002$). A statistically significant difference favoring ertapenem over cefotetan with respect to the primary endpoint has been observed at a significance level of 5% in this study. A second adequate and well-controlled study to confirm these

findings has not been conducted; therefore, the clinical superiority of ertapenem over cefotetan has not been demonstrated.

Pediatric Patients

Ertapenem was evaluated in pediatric patients 3 months to 17 years of age in two randomized, multicenter clinical trials. The first study enrolled 404 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ceftriaxone (50 mg/kg/day IV in two divided doses in patients 3 months to 12 years of age and 50 mg/kg/day IV as a single daily dose in patients 13 to 17 years of age) for the treatment of complicated urinary tract infection (UTI), skin and soft tissue infection (SSTI), or community-acquired pneumonia (CAP). Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of up to 14 days of treatment (parenteral and oral). The microbiological success rates in the evaluable per protocol (EPP) analysis in patients treated for UTI were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftriaxone. The clinical success rates in the EPP analysis in patients treated for SSTI were 95.5% (64/67) for ertapenem and 100% (26/26) for ceftriaxone, and in patients treated for CAP were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftriaxone.

The second study enrolled 112 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ticarcillin/clavulanate (50 mg/kg for patients <60 kg or 3.0 g for patients >60 kg, 4 or 6 times a day) up to 14 days for the treatment of complicated intra-abdominal infections (IAI) and acute pelvic infections (API). In patients treated for IAI (primarily patients with perforated or complicated appendicitis) the clinical success rates were 83.7% (36/43) for ertapenem and 63.6% (7/11) for ticarcillin/clavulanate in the EPP analysis. In patients treated for API (post-operative or spontaneous obstetrical endomyometritis, or septic abortion) the clinical success rates were 100% (23/23) for ertapenem and 100% (4/4) for ticarcillin/clavulanate in the EPP analysis.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-337
Submission Code	S-021, SE1
Letter Date	November 9, 2005
Stamp Date	November 10, 2005
PDUFA Goal Date	September 10, 2006
Reviewer Name	Peter W. Kim, M.D., M.S.
Review Completion Date	June 23, 2006
Revision Date	July 18, 2006
Established Name	Ertapenem Sodium
Trade Name	INVANZ®
Therapeutic Class	carbapenem
Applicant	Merck Research Laboratories
Priority Designation	S
Formulation	Parenteral (Intravenous)
Dosing Regimen	1000 mg once
Indication	Surgical Site Infection Prophylaxis in Elective Colorectal Surgery Patients
Intended Population	Adults aged ≥ 18 years old

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Applicant has submitted one adequate and well-controlled trial demonstrating that INVANZ® (ertapenem) 1 gram IV is noninferior to cefotetan 2 grams IV given 60 minutes prior to the initial surgical incision as a single dose infused over 30 minutes for the prophylaxis of surgical site infection following elective colorectal surgery. The overall safety profile for ertapenem in this trial was similar to that of cefotetan and is consistent with the current ertapenem labeling. The most frequently reported drug-related adverse event in patients receiving ertapenem was wound infection.

From a clinical perspective, the recommended regulatory action for this efficacy supplement is approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Ertapenem was approved in the United States in 2001 for other indications, and no changes in current postmarketing requirements are indicated.

1.2.2 Required Phase 4 Commitments

From a clinical standpoint, no Phase 4 commitments are indicated.

1.2.3 Other Phase 4 Requests

From a clinical standpoint, no Phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The trade name is: INVANZ®. The generic name is: ertapenem sodium (ertapenem). The drug class is: carbapenem. The route of administration for this supplement to NDA (sNDA) 21-337 is: intravenous (IV). The indication studied for this sNDA is: prophylaxis of surgical site infection following elective colorectal surgery. The proposed product was studied in adults aged 23 to 92 years old. Efficacy was established in adults aged 23 to 92 years old. One thousand and two patients were enrolled in this single trial to assess the safety and efficacy of ertapenem in

patients undergoing elective colorectal surgery. A total of 476 patients were exposed to ertapenem in this study. The reader is referenced back to the original clinical review of NDA 21-337 for additional information on the overall safety and efficacy found with ertapenem for the indications previously studied.

1.3.2 Efficacy

Study 039 was a multicenter, randomized, double-blind trial that compared a single dose of ertapenem 1 gram IV with cefotetan 2 grams IV for the prophylaxis of surgical site infection following elective colorectal surgery. The Agency's primary endpoint for this trial was clinical outcome at the post-treatment follow-up assessment visit 4 weeks after surgery (test-of-prophylaxis); analyses of the clinically evaluable and modified intent-to-treat (MITT) populations were considered co-primary. The Agency's secondary efficacy endpoints included the following. (1) The proportion of patients with a distant site infection any time up to the 4-week post-treatment visit. (2) The proportion of patients who developed the presence of microbiologic pathogens (any pathogen and for each pathogen).

This study enrolled 1002 patients, with 500 patients randomized to receive ertapenem and 502 randomized to receive cefotetan. There were discrepancies in the Applicant's and Medical Officer's evaluability determinations; however these did not affect the overall approvability of the application. In the Medical Officer's clinically evaluable population, cure rates at the 4-week follow-up visit (test-of-prophylaxis) adjusted for surgical procedure were 70.6% (244/346) for ertapenem and 57.3% (194/339) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 13.3% (95% confidence interval (CI), (6.1, 20.4). In the Applicant's original assessment of the clinically evaluable population, cure rates at the 4-week follow-up visit adjusted for surgical procedure were 72.0% (243/338) for ertapenem and 57.2% (191/334) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 14.8% (95% confidence interval (CI), (7.5, 21.9). In the Medical Officer's clinically evaluable population, the observed cure rates at the 4-week follow-up visit were 70.5% (244/346) for ertapenem and 57.2% (194/339) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 13.3% (95% confidence interval (CI), (6.1, 20.4). In the Applicant's original assessment of the clinically evaluable population, the observed cure rates at the 4-week follow-up visit were 71.9% (243/338) for ertapenem and 57.2% (191/334) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 14.7% (95% confidence interval (CI), (7.5, 21.8). On January 6, 2006, the Medical Officer provided a list of changes in patient evaluability based on a blinded review of 15% of case report forms (CRFs) and targeted review of over 140 additional CRFs. On February 17, 2006, the Applicant provided concurrence with the Medical Officer's evaluability changes and revised their efficacy analyses. The Applicant's revised efficacy analyses concurred with the Medical Officer's findings as noted above. (Because there were no significant differences between the prophylaxis rates in the observed and adjusted analyses, and for the sake of clarity of derivation of numbers, the observed results are reported in the label.) In the Medical Officer's MITT population, prophylaxis rates at the 4-week follow-up visit adjusted for surgical procedure were 58.4% (263/451) for ertapenem and 48.8% (220/450) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 9.6% (95% confidence interval (CI), (3.1, 16.0). In the Applicant's MITT population, cure rates at the 4-week follow-up visit adjusted for surgical

procedure were 58.4% (263/451) for ertapenem and 48.8% (220/450) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 9.6% (95% confidence interval (CI), (3.1, 16.0). In the Medical Officer's MITT population, the observed cure rates at the 4-week follow-up visit were 58.3% (263/451) for ertapenem and 48.9% (220/450) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 9.4% (95% confidence interval (CI), (2.9, 15.9). In the Applicant's MITT population, the observed cure rates at the 4-week follow-up visit were 58.3% (263/451) for ertapenem and 48.9% (220/450) for cefotetan; the treatment difference (ertapenem minus cefotetan) was 9.4% (95% confidence interval (CI), (2.9, 15.9). The secondary efficacy endpoint analyses were generally consistent with the primary endpoint analyses.

In Study 039, the Applicant demonstrated that a single intravenous dose of ertapenem 1 gram given 1 hour prior to surgical incision was noninferior to a single intravenous dose of cefotetan 2 grams given 1 hour prior to surgical incision for prophylaxis against surgical site infections in elective colorectal surgery patients. The results of this study support the approval of ertapenem for prophylaxis of surgical site infections following elective colorectal surgery.

1.3.3 Safety

In Study 039, 476 patients received one dose of ertapenem, and 476 patients received one dose of cefotetan. The dose of ertapenem in this study is the same as is found in the approved labeling for complicated intra-abdominal infections and complicated skin and skin structure infections, as well as for the other infectious disease indications for which ertapenem is currently indicated for treatment in adult patients with normal renal function. Because the proposed prophylactic indication is a single 1 gram dose of ertapenem, no dose adjustment will be made for patients with impaired renal function.

Adverse events were recorded from study drug administration through to 14 days post-treatment. Laboratory testing of hematologic status and renal and hepatic function was performed within 30 days prior to study therapy, 48 hours prior to surgery, at least once post-operatively at Day 3-4 (or earlier if the patient was to be discharged before Day 3-4) and as clinically indicated, and at the 4-week follow-up visit if clinically indicated. One of the Applicant's pre-specified secondary endpoints was assessing the proportion of patients with any drug-related adverse events.

The most frequently reported adverse events (AEs) in patients receiving ertapenem were nausea, pyrexia, ileus, vomiting, wound infection, and pruritus. The most frequently reported drug-related AE in patients receiving ertapenem was wound infection. The overall safety profile for ertapenem was similar to that of cefotetan and is consistent with the current ertapenem labeling.

1.3.4 Dosing Regimen and Administration

The proposed adult dosing regimen of a single 1 gram dose of ertapenem administered intravenously 60 minutes prior to surgical incision, is effective for prophylaxis of surgical site infections following elective colorectal surgery.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was identified.

1.3.6 Special Populations

No new information has been obtained related to special populations. The reader is referred back to the original clinical review of NDA 21-337 for detailed information on this topic.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Established Drug Name

Ertapenem Sodium

2.1.2 Proposed Trade Name

INVANZ®

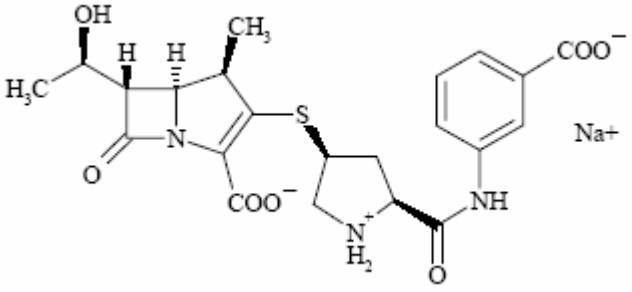
2.1.3 Chemical name

[4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid monosodium salt

2.1.4 Molecular formula

$C_{22}H_{24}N_3O_7SNa$

2.1.5 Chemical Structure



2.1.6 Drug Class

Carbapenem

2.1.7 Applicant's Proposed Indication

Prophylaxis of surgical site infection following elective colorectal surgery

2.1.8 Dose

One-time dose of 1 gram intravenously

2.1.9 Mechanism of Action

Ertapenem is a long-acting parenteral 1-β-methyl carbapenem antibiotic characterized by a broad spectrum of antibacterial activity against both gram-positive and gram-negative aerobic and anaerobic bacteria. The antibacterial activity of ertapenem is targeted at the inhibition of bacterial cell-wall synthesis by binding to specific penicillin-binding proteins (PBPs). This action results in growth inhibition and, with very few exceptions, rapid cellular lysis and death. The presence of a methyl group at C1 confers stability to human renal dehydropeptidase-1 enzyme, and a hydroxyethyl side chain at C6 confers resistance against a variety of β-lactamases.

2.1.10 Regimen

The proposed regimen is a single, 1 gram dose by intravenous (IV) route infused over 30 minutes and given 60 minutes prior to the initial surgical incision.

2.1.11 Age Groups

For the indication of surgical site infection prophylaxis following elective colorectal surgery, the Applicant states that ertapenem may be safely used in patients aged 18 years and older.

2.2 Currently Available Treatment for Indication

Several currently available antibacterial agents are approved for prophylaxis or prevention of surgical site infection after clean contaminated or potentially contaminated surgery. The following Table 1A, is entitled, "Currently Available Antibacterial Agents with Specific Language in Labeling for Prophylaxis or Prevention of Surgical Site Infection after Clean Contaminated or Potentially Contaminated Surgery."

Table 1A. Currently Available Antibacterial Agents with Specific Language in Labeling for Prophylaxis or Prevention of Surgical Site Infection after Clean Contaminated or Potentially Contaminated Surgery

Drug Product	Specific Indication(s)[1]	Recommended Dose[1]
Ceftriaxone	Surgical Prophylaxis: "in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., ...cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common bile duct stones)..."	A single 1 gram dose IV 30 mins to 2 hrs before surgery
Cefotaxime	Prevention: "in patients undergoing surgical procedures (e.g., ...gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated."	A single 1 gram IM or IV administered 30 to 90 mins prior to start of surgery
Cefuroxime	Prevention: "in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures."	1.5 grams IV 30 to 60 mins before the initial incision followed by 750 mg IV or IM every 8 hrs when the procedure is prolonged.
Cefazolin	Perioperative prophylaxis: "in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g., ...cholecystectomy in high risk patients such as those over 70 years of age who have acute cholecystitis, obstructive jaundice, or common-bile-duct stones"	1 gram IV or IM 30 to 60 mins prior to start of surgery. For surgeries lasting 2 or more hrs, administer 500 mg to 1 gram IV or IM during surgery. May give 500 mg to 1 gram IV or IM every 6 to 8 hours for 24 hrs postoperatively.
Metronidazole	Prophylaxis: "in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated"	15 mg/kg infused IV over 30 to 60 mins and completed approximately 1 hr before surgery; followed by 7.5 mg/kg infused over 30 to 60 mins at 6 and 12 hrs after the initial dose
Cefotetan	Prophylaxis: "in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (e.g., ...gastrointestinal surgery)."	A single 1 or 2 gram dose IV 30 to 60 mins prior to surgery

[1] Please refer to individual product labeling for complete language on specific indications and recommended dose.
IV = intravenous, IM = intramuscular, mins = minutes, hr = hour

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

INVANZ® is currently marketed in the United States for the following indications:

"**Complicated Intra-abdominal Infections** due to *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteroides disasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron,* or *Bacteroides uniformis.*

Complicated Skin and Skin Structure Infections including diabetic foot infections without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible (b) (4) only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*.

Community Acquired Pneumonia due to *Streptococcus pneumoniae* (penicillin-susceptible (b) (4) only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative (b) (4) only), or *Moraxella catarrhalis*.
Complicated Urinary Tract Infections including pyelonephritis due to *Escherichia coli,* including cases with concurrent bacteremia, or *Klebsiella pneumoniae*.
Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia*."

Major safety concerns include: (1) serious and occasionally fatal hypersensitivity (anaphylactic) reactions among patients with previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens; (2) seizures and other CNS adverse experiences have been reported during treatment with ertapenem; and (3) pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening.

Labeling changes include:

April 30, 2004	The following was added to the *Post-Marketing Experience* subsection of the ADVERSE REACTIONS section of the label: "The following post-marketing adverse experiences have been reported: *Immune System:* anaphylaxis including anaphylactoid reactions, *Nervous System & Psychiatric:* hallucinations."
May 20, 2004	Revised labeling was added to comply with the FDA's Final Rule entitled, "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use (21 CFR Part 201)," published on February 6, 2003 (68 FR 6062).
September 10, 2004	The following microorganisms were added to the CLINICAL PHARMACOLOGY section, Microbiology subsection: *Staphylococcus epidermidis* (methicillin susceptible strains only), *Providencia rettgeri*, *Providencia stuartii*, and *Bacteroides vulgatus*.
May 18, 2005	Merck gained regulatory approval for pediatric dosing of ertapenem in patients as young as 3 months. The following sections were updated to include information on pediatric patients: CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, PREPARATION OF SOLUTION, and CLINICAL STUDIES.
October 14, 2005	Merck gained regulatory approval for the Complicated Skin and Skin Structure Infections sub-indication of diabetic foot infections

without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible (b) (4) only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*. The following sections were updated: CLINICAL PHARMACOLOGY (*Microbiology* subsection), INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, (b) (4), and CLINICAL STUDIES.

2.4 Important Issues With Pharmacologically Related Products

(b) (4)

NDA 50,587 and NDA 50,630
Imipenem (PRIMAXIN® I.V. supplied by Merck), available for intravenous or intramuscular administration, received FDA approval in 1985. Imipenem is currently approved for the indications of "lower respiratory tract infections," "urinary tract infections (complicated and uncomplicated)," "intra-abdominal infections," "gynecologic infections," "bacterial septicemia" (due to *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species, *Bacteroides* species including *B. fragilis*), "bone and joint infections," "skin and skin structure infections," "endocarditis," and "polymicrobic infections" [including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or non-penicillinase-producing *S. aureus* is one of the causative organisms].

While imipenem has been associated with safety concerns common to most beta-lactam antimicrobials (e.g., diarrhea, nausea, liver function abnormalities, increased creatinine, etc.), notably its use has also been associated with seizures and other central nervous system (CNS) adverse experiences, such as confusional states and myoclonic activity. Although in the imipenem safety database, CNS adverse experiences occurred most commonly in patients with underlying CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function, there were reports of CNS events in patients with no known underlying CNS disorders or renal impairment. In the Primaxin® I.V. label, "seizures" are reported with an incidence of 0.4% (reported as possibly, probably, or definitely related adverse clinical reactions). Of note, the label for imipenem includes the listing of "pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, …" in the Adverse Reactions section of the label.

NDA 50,706 (b) (4)
Meropenem (MERREM I.V. supplied by AstraZeneca) originally received approval in 1996. Meropenem is currently approved for the indications of "complicated skin and skin structure infections" (as of May 17, 2005), "intra-abdominal

infections-complicated appendicitis and peritonitis" in adults (with pediatric dosing recommendations provided) and "bacterial meningitis" in pediatric patients ≥ 3 months. The (b) (4) .

Meropenem has also been associated with safety concerns common to most beta-lactam antibacterials (e.g., diarrhea, nausea, liver function abnormalities, increased creatinine, etc.), and like imipenem, its use has also been associated with seizures and other CNS adverse experiences. In the meropenem safety database (in 2904 patients with infections outside the CNS), seizures occurred in 0.7%. All meropenem-treated patients with seizures had underlying CNS disorders (e.g., brain lesions or history of seizures) or had received concomitant medications with seizure potential. Of note, the FDA has recommended and the Applicant has accepted the following revision in the post-marketing Adverse Reactions section of the label for meropenem, "Hematologic-agranulocytosis, neutropenia, and leukopenia."

(b) (4)

(b) (4)

2.5 Presubmission Regulatory Activity

August 3, 1995	Applicant submitted IND 48,485 for MK-0826 (subsequently named ertapenem sodium, tradename: INVANZ®.
November 30, 2000	Applicant submitted NDA 21,337 for review on a 10 month review clock.
November 6, 2001	Applicant submitted Serial No. 379, Protocol 039, entitled, "A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and

	Efficacy of a Single Dose of Ertapenem Sodium (MK-0826) Versus Cefotetan for the Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery."
November 21, 2001	The Applicant received approval for the following five indications: "**Complicated Intra-abdominal Infections** due to *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteroides disasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron,* or *Bacteroides uniformis.* **Complicated Skin and Skin Structure Infections** due to *Staphylococcus aureus* (methicillin-susceptible only), *Streptococcus pyogenes, Escherichia coli,* or *Peptostreptococcus* species.***** **Community Acquired Pneumonia** due to *Streptococcus pneumoniae* (penicillin-susceptible strains only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative strains only), or *Moraxella catarrhalis*. **Complicated Urinary Tract Infections including pyelonephritis** due to *Escherichia coli,* including cases with concurrent bacteremia, or *Klebsiella pneumoniae*. **Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections** due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia*." *****However, the Division determined that the Applicant provided insufficient data to support the sub-indication of diabetic foot infection (DFI). The Division later granted the DFI sub-indication on 10/14/05 upon completing review of new clinical data provided in Study 034.
December 11, 2001	The Division faxed the Applicant suggestions for protocol revisions, including amending the protocol to lower the non-inferiority delta margin from 15% to 10% and increasing the sample size appropriately.
March 13, 2002	The Applicant submitted revisions to Protocol 039 that included requested changes to the non-inferiority delta margin and increasing the sample size of the study population.
October 29, 2004	The Applicant submitted the Data Analysis Plan (DAP) for Protocol 039.
December 7, 2004	The Division provided comments on the DAP for Protocol 039. These included: (1) stating that the Division would view the "evaluable-patients-only" and "modified intent-to-treat" populations as co-primary; (2) clarification on criteria for treatment

	failure and exclusion in the MITT analysis, as well as how missing data would be handled in the MITT analysis; and (3) reiteration of an April 25, 2002 request for a sensitivity analysis for efficacy outcome by renal function.
March 10, 2005	The Applicant submitted a revised DAP for Protocol 039.
April 11, 2005	The Division provided additional comments on the revised DAP for Protocol 039. These included: (1) stating that the Division would view subjects receiving concomitant antimicrobial therapy to treat a distant site of infection as nonevaluable for the clinically evaluable (per protocol) analysis and as indeterminate for the MITT analysis; (2) clarification that patients who developed a distant site of infection and subsequently developed a surgical site infection and returned for the 4-week follow-up visit would be considered a failure for the MITT analysis; and (3) reiteration of the December 7, 2004 Division comment that the Division would view the "evaluable-patients-only" and "modified intent-to-treat" populations as co-primary

2.6 Post-submission Regulatory Activity

December 27, 2005	The Division requested: (1) sensitivity analyses of clinical efficacy stratified on whether: (a) the duration from study drug infusion to end of surgery was $\leq$ or > 4 hours, and (b) the duration from study drug infusion to start of surgery was $\leq$ or > 60 minutes; and (2) line listings of microbiology data from Study 039, specifically; bacterial species isolated per patient, source of clinical isolate, microscopy information, susceptibility data, and quality control data from reference laboratories.
January 6, 2006	The Division provided the Applicant with a list of discrepancies with the evaluability of specific patients based on differences between what was stated in the Applicant's Data Analysis Plan (DAP) and Clinical Study Report (CSR) and how the Applicant actually treated specific patients in the study. The Applicant provided a response on February 17, 2006. The Applicant agreed that 13 patients (8 in the ertapenem group and 5 in the cefotetan group) were incorrectly made nonevaluable. These patients were changed to evaluable.
March 1, 2006	The Applicant provided an explanation as to why the prophylactic success rate in the cefotetan arm was significantly lower than in previous studies of prophylaxis against surgical site infections in

	elective colorectal surgery patients. The Applicant pointed to more stringent criteria for failure, inclusion of different surgical procedures, and increased prevalence of obesity within the study cohort as possible explanations for the lower prophylaxis response rate as compared with prior studies.
April 27, 2006	The Applicant provided a correction to the MITT prophylactic success rates. Due to a programming error, six ertapenem patients and one cefotetan patient with distant site infections were incorrectly categorized as success of prophylaxis for the MITT analysis. These changes had no effect on the prophylactic success rates for the clinically evaluable population and had a minimal effect on the results for the MITT analysis.

2.7 Other Relevant Background Information

The Applicant states that ertapenem has been in marketed use since it was first approved for adult use in Mexico on March 30, 2001. Ertapenem is currently registered and approved in 66 countries. The marketing approval of ertapenem has not been suspended, revoked, or withdrawn by any regulatory agency in any country. There have been no regulatory actions related to safety.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information related to chemistry, manufacturing and controls or product microbiology was included in this submission.

3.2 Animal Pharmacology/Toxicology

No new information related to animal pharmacology/toxicology was included in this submission. The reader is referred back to the original animal pharmacology/toxicology review of NDA 21-337 for detailed information on this topic.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Applicant conducted one clinical study, Study 039, in support of the prophylaxis of surgical site infection following elective colorectal surgery indication. It should be noted that the Applicant's product was already found to be generally safe and effective for five indications, including complicated intra-abdominal and complicated skin and skin structure infections in the original clinical review of NDA 21-337.

The following additional materials were consulted in the review of this NDA.

1. Original clinical reviews of NDA 21-337
2. Literature as referenced throughout and noted at the end of this review.

4.2 Table of Clinical Study

Table 1. Listing of Clinical Study

Study Number	Population	Test Drugs	Patient Enrollment	Mean Duration of Exposure (Days)	Range of Exposure (Days)
039	Elective colorectal surgery patients	Ertapenem 1 gm x 1 dose	500	1	1
		Cefotetan 2 gm x 1 dose	502	1	1

4.3 Review Strategy

Detailed reviews of the data from Study 039 are presented in the integrated reviews of efficacy (section 6) and safety (section 7) for the indication of prophylaxis of surgical site infection following elective colorectal surgery. It should be noted that the Applicant's product was already found to be generally safe and effective for five indications, including complicated intra-abdominal and complicated skin and skin structure infections in the original clinical review of NDA 21-337.

4.4 Data Quality and Integrity

This Medical Officer performed a blinded review of a random sample of 15% of the case report forms (CRFs) from Study 039 to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with the Applicant's evaluability and outcome determinations. The results of this initial survey led to a more extensive review of more than 140 additional CRFs. The CRF review is discussed in detail in section 6.

The DAIOP did not request that the Division of Scientific Investigation (DSI) perform any additional data audits.

Medical Officer's comment: ***In general, the M.O. found the data quality acceptable.***

4.5 Compliance with Good Clinical Practices

With regard to Study 039, the Applicant stated that institutional review board approval was obtained for each center, that the studies were conducted according to ethical principles originating in the Declaration of Helsinki and consistent with International Conference of Harmonization good clinical practice guidance, and that informed consent was obtained from all patients before the start of any study procedures.

4.6 Financial Disclosures

The Applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) stating that it had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study. As shown in Table 2 below, the Applicant reported that there were 6 investigators/subinvestigators with disclosable financial interests.

Table 2. All Investigators/Subinvestigators Who Hold Financial Interests Requiring Disclosure (Adapted from Applicant's Table D-1 on page 23 of the Financial Information section of sNDA 21-337/Study 039)

Protocol/Site	Investigators/Subinvestigators	Financial Interest
	(b) (6)	$92,028.93 in "Significant Payments of Other Sorts"
		$36,805.92 in "Significant Payments of Other Sorts"
		$59,259.00 in "Significant Payments of Other Sorts"
		$31,878.00 in "Significant Payments of Other Sorts"
		$32,195.00 in "Significant Payments of Other Sorts"
		$32,202.00 in "Significant Payments of Other Sorts"

The Applicant states on page 1 of the Financial Information section of sNDA 21-337/Study 039 that, "significant payments of other sorts" are calculated cumulatively when an investigator is involved in more than one protocol in a submission.

In addition, the Applicant disclosed that 4 subinvestigators from 4 sites failed to respond to "multiple requests" for financial disclosure information.

Medical Officer's comments: ***For the six study sites where investigators/subinvestigators disclosed significant financial interests (sites*** (b) (6)***), the M.O. evaluated for high enrollment and evaluability, as well as for discrepancies in patient evaluability and outcome. Table 3 illustrates that none of the six sites enrolled more than*** (b) (6) ***of the total clinical MITT set. Therefore, results from these sites would have minimal effect on the primary endpoint of Study 039.***

Table 3. Study Details for the Six Sites with Investigators/Subinvestigators Who Hold Financial Interests Requiring Disclosure

Site No.	No. of clinical MITT patients enrolled		% of total clinical MITT set	No. of FUA clinical evaluable patients enrolled per Applicant		No. of FUA clinical evaluable patients enrolled per M.O.		Clinical success rate (%) for FUA evaluable per Applicant		Clinical success rate (%) for FUA evaluable per M.O.	
	E	CT		E	CT	E	CT	E	CT	E	CT
(b) (6)								50	60	50	60
								73	50	73	50
								69	76	61	76
								NA	100	NA	100
								100	NA	100	0
								0	50	0	50

E= Ertapenem, CT= Cefotetan, NA= Not Applicable

A total of 73 patients were enrolled from the four study sites where a total of 4 subinvestigators failed to respond to the Applicant's multiple requests for financial disclosure information. This represented 7.3% of the total clinical MITT set. Therefore, results from these sites would have minimal effect on the primary endpoint of Study 039.

Beyond these issues, the M.O. considered the financial disclosures adequate.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new information has been obtained related to pharmacokinetics in adults. The reader is referred back to the original clinical pharmacology review of NDA 21-337 for detailed information on this topic. Notably, there was no dose adjustment for patients with impaired renal function when ertapenem was given as a single intravenous dose one hour prior to elective colorectal surgery for prophylaxis against surgical site infection.

5.2 Pharmacodynamics

No new information has been obtained related to pharmacodynamics in adults. The reader is referred back to the original clinical pharmacology review of NDA 21-337 for detailed information on this topic.

5.3 Exposure-Response Relationships

No new information has been obtained related to exposure-response relationships in adults. The reader is referred back to the original clinical pharmacology review of NDA 21-337 for detailed information on this topic.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Prophylaxis of surgical site infection following elective colorectal surgery

The Applicant proposes the following labeling claim change:

> INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

6.1.1 Methods

The Applicant performed one clinical efficacy trial to support the indication of prophylaxis of surgical site infection following elective colorectal surgery. Study 039, entitled, "A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of a Single Dose of Ertapenem Sodium (MK-0826) Versus Cefotetan for the Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery," was a multicenter, randomized, double-blind trial intended to demonstrate the noninferiority of ertapenem to the approved comparator, cefotetan, for prophylaxis of surgical site infection following elective colorectal surgery in patients $\geq$ 18 years of age. The final protocol was dated March 13, 2002 and submitted to the Agency on March 20, 2002. The first patient was enrolled May 6, 2002, and the final patient completed the study March 9, 2005. This trial was reviewed in detail in the sections that follow.

6.1.2 General Discussion of Endpoints

The Applicant stated, on page 32 and 45 of the Clinical Study Report (CSR), that the primary endpoint of Study 039 was the proportion of patients who had a favorable clinical outcome at the 4-week post-treatment follow-up visit (test-of-prophylaxis). The Sponsor considered patients as having favorable outcomes if the following criteria were met: (1) no signs/symptoms of surgical site infection, (2) no further antimicrobial therapy was necessary, and (3) no surgical intervention for infection was necessary. Secondary efficacy endpoints included the following. (1) The proportion of patients with a distant site infection any time up to the 4-week post-treatment visit. (2) The proportion of patients who developed the presence of microbiologic pathogens (any pathogen and for each pathogen).

Medical Officer's comments: There is currently no regulatory guidance provided for the indication of prophylaxis of surgical site infection in elective colorectal surgery patients. Neither the 1992 nor the 1997 Division of Anti-Infective Drug Products (DAIDP) "Points to Consider" documents discuss this indication. However, a joint effort by the IDSA and FDA derived guidelines for colorectal surgical prophylaxis.[1] The guidelines distinguish between prophylaxis (within 12 hours of surgery) and treatment (> 12 hours from the time of surgery

after the development of signs of serious infection, such as septic shock, abscess formation, or diffuse peritonitis) when using an anti-infective product.

Three different surgical conditions exist when one considers the need for anti-infective prophylaxis:

1. "contaminated or dirty" operations: gun-shot wound, perforation of the gastrointestinal tract (ruptured appendix, perforated diverticulum)

2. "clean contaminated" operations: vaginal hysterectomy and colorectal operations

3. "clean" operations where prophylaxis is not justified: mastectomy, inguinal hernia repair

According to the guidance, an anti-infective drug product under development for surgical prophylaxis should meet the following objectives:

- ***Prevent postoperative infectious morbidity and mortality***
- ***Reduce the length and cost of hospital care***
- ***Be the cause of minimal adverse effects on the microbial flora of the patient or hospital (e.g., the promotion of antimicrobial resistance)***
- ***Active against the pathogens most likely to contaminate the wound***
- ***Given in appropriate doses, and at a time that ensures adequate concentrations at the incision site during the potential period of contamination***
- ***Safe***
- ***Administered for the shortest effective period to minimize cost and adverse drug effects***
- ***Additional measures to reduce infection such as pre-operative skin antisepsis, wound irrigation (preferably without antibiotics), prophylactic drainage, or variations in surgical technique should be clearly identified in the protocol, should be standardized insofar as possible, and should be recorded in the course of the study***
- ***In general, the first dose of a parentally-administered antibiotic should be selected to achieve peak target concentrations in the primary surgical site at the time of the initial incision.***
- ***Although not required for evaluability, it is highly desirable to record antimicrobial resistance patterns of infecting pathogens in both treatment and control groups in order to analyze for evidence of "emergence" of resistance***
- ***Duration of follow-up should be clearly defined and appropriate to surgical procedure. Ordinarily, a 4-week follow-up is sufficient.***

According to the guidelines, risk factors for postoperative infection in colorectal operations include the following:

- ***Rectal resections (abdominal-perineal resections) are associated with higher rates of infection than intra-peritoneal resections.***
- ***Operations lasting more than 3.5 to 4 hours are associated with more infections than those of shorter duration.***
- ***Inadequate bowel preparation (e.g., isotonic lavage solution)***

- ***Emergency surgical procedures***

Failure of Prophylaxis (as defined in the IDSA/FDA Guidelines):

- ***Postoperative infection within the primary operative incision and/or the peritoneal cavity, including peritonitis and abscess formation.***
    - ***Infection developing in the primary operative incision(s) should be classified as failure of antimicrobial prophylaxis.***
    - ***Infection developing in a distant site (e.g., urinary tract, respiratory tract, IV catheter, etc.) should be reported but not included in the criterion of success or failure of prophylaxis.***
- ***Any unexplained use of anti-infective agents in the 4-week period following the primary operation.***
- ***Any drainage procedure at the operative site or in and around the peritoneal cavity for infection.***
- ***The development of an anastomotic leak.***

The guidelines noted that, "A minimum of 50 evaluable patients per participating site center is required."

In addition, the Medical Officer reviewed the Clinical Review for the most recent drug product to be granted approval for the indication of surgical site infection prophylaxis in elective colorectal surgery. TROVAN (trovafloxacin mesylate), NDAs 20-759 (oral tablets) and 20-760 (intravenous) was approved on December 18, 1997. In Study 154-128, a randomized, double-blind, double-dummy, multicenter study, TROVAN 200 mg IV was compared with cefotetan 2 grams IV. TROVAN was administered within 2 hours of surgery and infused over 1 hour. Cefotetan was given 30-60 minutes prior to surgery and infused over 1 hour. Two-hundred fifty-six patients received TROVAN and 236 received cefotetan. Failure of prophylaxis was defined in a similar manner to the current INVANZ study (Protocol 039) and included: (1) development of infection in the primary operative site, (2) development of an unexplained fever requiring systemic antibiotic intervention, (3) use of any systemic anti-infective drug during the 30-day post-operative period for treatment of infection (suspected or confirmed) at the primary site, (4) any unexplained use of anti-infective agents in the 30-day period following the primary operation, (5) missing post-baseline assessment, (6) any drainage procedure at the operative site or in and around the peritoneal cavity for infection, and (7) need for more than one surgical procedure.

The criteria for failure of the primary endpoint were very similar to the current protocol, Study 039. Inclusion, exclusion, and evaluability criteria were also very similar between Study 039 and the TROVAN Study 154-128.

On 12/7/04 and 4/11/05, the FDA stipulated that the 4-week follow-up clinical outcomes (test-of-prophylaxis) in both the clinically evaluable (Evaluable) and clinical modified intent-to-treat (MITT) populations would be considered co-primary. The Applicant agreed to provide these data.

From the perspective of the Agency, the analyses used to assess the efficacy and ultimately the approvability of ertapenem (pending adequate demonstration of safety in the proposed population) were:

1. ***Primary Analysis (test-of-prophylaxis):***
    a. ***The proportion of subjects who had a favorable clinical outcome at the 4-week post-treatment follow-up visit. Patients had to meet all of the following criteria: (1) no signs/symptoms of surgical site infection, (2) no further antimicrobial therapy was necessary, and (3) no surgical intervention for infection was necessary.***
        i. ***As co-primary: the result of the test-of-prophylaxis analysis in the clinical modified intent-to-treat (MITT) population should be consistent with that found in the clinically evaluable population.***
2. ***Secondary Analyses:***
    a. ***The proportion of patients with a distant site infection any time up to the 4-week post-treatment visit.***
    b. ***The proportion of patients who developed the presence of microbiologic pathogens (any pathogen and for each pathogen).***

The results of these analyses were emphasized in this review.

6.1.3 Study Design

6.1.3.1 Population

Inclusion Criteria (taken from page 38 of the CSR)

This study included patients ≥ 18 years of age who underwent elective colon or colorectal surgery by laparotomy meeting the following criteria:

1. Surgery must be scheduled in advance.
2. There must be adequate time to complete preoperative bowel preparation.

Medical Officer's comments: The inclusion criteria were generally acceptable.

Exclusion Criteria (taken from pages 38-40 of the CSR)

1. Failure to meet all inclusion criteria.
2. Patients with emergency colon or colorectal surgery (unscheduled surgery with insufficient time to complete preoperative bowel preparation).

3. Patients who were to undergo a second planned colorectal surgery or other surgery requiring antibiotic prophylaxis within the 4-week follow-up period.

4. Patients undergoing laparoscopic assisted surgery.

5. Patients undergoing an isolated rectal procedure.

6. Patients with decompensated intestinal obstruction.

7. Patients with active inflammatory bowel disease involving the colon.

8. Patients scheduled to undergo an elective colorectal procedure for revision of a previous operation involving large bowel resection (e.g., revision of a colostomy or ileo-rectal anastomosis).

9. Patients with a bacterial infection at the time of surgery or with a need for administration of systemic antimicrobial therapy within 1 week prior to surgery.

10. Patients requiring antimicrobial prophylaxis for subacute bacterial endocarditis or other condition.

11. Coexisting condition at baseline that required antimicrobial therapy during the course of the study.

12. Patients with a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to carbapenem antibiotics (such as imipenem), cefotetan, any cephalosporins or other β-lactam agents. Patients with history of mild rash to cephalosporins or other β-lactams may be enrolled.

13. Patients with a history of cephalosporin associated hemolytic anemia.

14. Pregnant women, nursing women, women of childbearing potential not practicing adequate methods of contraception, or women planning to become pregnant within 1 month of the study. NOTE: Females of childbearing potential must have a negative serum pregnancy test (β-hCG) prior to enrollment into the study and must use adequate birth control measures as discussed with the investigator for at least 1 month after study treatment.

15. Patients with transaminase levels (ALT or AST) $\geq$ 3 times the upper limit of the range of normal values used by the laboratory performing the test (ULN).

16. Patients requiring hemodialysis or hemofiltration.

17. Neutropenia with absolute neutrophil count (ANC) < 1000/mm^3.

18. Coagulation (prothrombin time [PT] and partial thromoplastin time [PTT] and/or INR) tests greater than the upper limit of the range of normal values used by the laboratory performing the test (ULN). Patients who are on anticoagulant therapy with values > the ULN may be enrolled, provided these values are corrected to within the normal range prior to the surgical procedure.

19. Patients with immunosuppression due to an underlying disease, chronic immunosuppressive therapy, or use of high-dose corticosteroids (e.g., 40 mg or more of prednisone or equivalent per day).

20. History of any illness that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drug to the patient.

21. Participation in any other clinical study involving the administration of investigational medication in the 30 days prior to enrollment. Previous participation in this study at any time.

22. Inability of the patient or legal representative to provide written informed consent for any reason.

Medical Officer's comment: The exclusion criteria were generally acceptable.

6.1.3.2 Study Procedures

Study Treatments

Patients were randomized to receive one of the following study therapies:

- Ertapenem, administered as a single 1-gram dose given within the 60 minutes prior to the planned initial incision and infused over 30 minutes
- Cefotetan, administered as a single 2-gram dose given within the 60 minutes prior to the planned initial incision and infused over 30 minutes

Medical Officer's comment: The dose regimen appeared adequate for the population of elective colorectal surgery patients studied.

The labeled dose of cefotetan for prophylaxis against surgical site infection is 1-2 grams IV administered 30 to 60 minutes prior to the incision.

No dosing adjustments were made for patients with renal impairment because this was a single dose study.

Treatment assignments were based on a randomization schedule created using computer-generated random numbers. At each site, patients were sequentially randomized to one of the two study regimens (ertapenem 1 gram IV or cefotetan 2 grams IV) in a 1:1 ratio, according to the allocation schedule. The randomization schedule was provided by the Applicant and given only to the study pharmacist or other individual who was to prepare IV study therapy for infusion. Eligible patients were assigned to treatment group by an allocation number from the randomization schedule by the pharmacist.

Patients scheduled to undergo an elective intraperitoneal surgical procedure were assigned an allocation number from Schedule A. Patients scheduled to undergo an elective abdominoperineal resection were assigned an allocation number from Schedule B.

This clinical trial studied prophylaxis against surgical site infection in elective colorectal surgery patients using a one-time dose of intravenous antibacterial therapy 30-60 minutes prior to surgical incision.

Medical Officer's comment: The M.O. noted that 148/346 (42.8%) of ertapenem patients and 119/339 (35.1%) of cefotetan patients received study therapy > 60 minutes up to 2 hours prior to surgical incision and were still considered evaluable. The prophylaxis response rates for this group of patients did not significantly differ from the prophylaxis response rates of the

patients who received their study therapy within 60 minutes prior to skin incision. Therefore the M.O. did not contest this deviation from the original study protocol. The M.O. discusses this issue in further detail in sections 6.1.3.4, 6.1.4.3, and 6.1.6

No concurrent systemic antibacterial therapy was permitted. Use of antibiotic and antiseptic peritoneal lavage during the operative procedure was not permitted.

Blinding

This was a double-blind study. Therefore, the investigator, study nurse, and patients remained blinded to the IV study therapy. The study pharmacist (or other individual who was to prepare IV study antibiotics for infusion) received open-label clinical supplies and an appropriate allocation schedule from the Applicant. The Applicant notes on page 42 of the CSR that study infusions of ertapenem are generally clear, colorless, and indistinguishable from cefotetan (or saline), but rarely, a slight color difference may be detected when the infusions are viewed along side each other. The Applicant instituted measures to ensure blinding. These included limits on time of reconstitution, choice of final infusion container, prompt disposal of study infusion bags, and use of amber-colored translucent IV cover bags.

Medical Officer's comments: In general, bias was minimized throughout the conduct of the study. However, the Applicant reserved the right to re-adjudicate evaluability after the blind was broken. This may have introduced bias into the final determination of patient evaluability. In an effort to decrease potential bias, the Agency stipulated that the MITT analysis be considered a co-primary endpoint. As such, the Agency proposes to include the results of the MITT analysis in the "CLINICAL STUDIES" section of the product label. The Medical Officer believes that to avoid this potential bias, future studies should not include re-adjudication of evaluability after the study blind is broken.

Choice of Control Group

On page 37 of the CSR, the Applicant states that cefotetan was chosen as the comparator because it is commonly used for prophylaxis against surgical site infections in elective colorectal surgery patients and has been previously shown to be safe and effective for this and other indications.

Medical Officer's comment: The M.O. considers the Applicant's choice of cefotetan for the active control group appropriate for the studied indication.

Microbiological Methods

These methods will be described in detail in the Division's Microbiology review. Please also refer to section 6.4, "Clinical Microbiology," of this review for additional details.

If a patient developed a postoperative infection either at the surgical site or at a remote site, appropriately obtained specimens from the site of infection were sent for culture (aerobic and anaerobic). In vitro susceptibility testing to ertapenem and cefotetan were performed for all organisms considered pathogens. Blood cultures (at least two sets) to test for bacteremia were performed if patients sustained a fever as defined by an oral temperature > 38.5°C (101.2°F) on two occasions at least 6 hours apart in a 24 hour period.

Study Evaluations (The following is summarized from the Applicant's table, entitled, "Schedule of Clinical Observations and Laboratory Measurements," found on page 36 of the CSR.)

Visit 1

A. Screening (within 30 days of study therapy)

- Collection of general patient information, including the nature and extent of the present illness requiring surgery
- Assessment of baseline risk factors for postoperative infection including diabetes, tobacco use (active or inactive) and obesity
- Physical examination
- Clinical laboratory tests (chemistry, hematology, urinalysis)
- Serum pregnancy test (if female of childbearing potential)

B. Preoperative/Pretreatment Evaluation (within 48 hours prior to surgery)

- If screening procedures occurred > 48 hours prior to study drug administration, then the medical history and physical exam were updated
- Clinical laboratory tests (chemistry, hematology, urinalysis) on day of surgery prior to administration of study drug
- Confirmation of adequate completion of bowel preparation regimen
- Temperature and vital signs [maximal or minimal (if < 35ºC or 95°F) pre-operative temperature of the day]

Visit 2

Day of Surgery

- Preoperative vital signs
- Details of surgical procedure recorded
    - Name/type of procedure
    - Underlying disease requiring surgery
    - Timing of study medication administration and initial surgical incision
    - Dosing record
    - Adequacy of mechanical bowel preparation
    - Placement of surgical drains
    - Duration of surgery
    - Use of wound protectors
    - Use of supplemental oxygen
    - Details of skin closure
    - Documentation of occurrence of inadvertent perforation or spillage of luminal contents
    - Documentation of requirement of adjuvant chemotherapy and/or radiation therapy during the 30 days prior to surgery

Visit 3

A. Every Other Day during Hospitalization (Up to 7 Days)

- Daily vital signs and monitoring for adverse events
- Surgical wound examination on every other day basis
- Wound and/or blood culture and susceptibility in event of postoperative infection
- Clinical laboratory tests at least once on post-op Day 3 or 4 and as clinically indicated

B. Day of Hospital Discharge

- Clinical assessment (vitals signs and physical examination, including evaluation of surgical wound)
- Monitoring for adverse events
- Clinical laboratory and microbiologic tests if indicated

- Clinical efficacy evaluation

Visit 4

A. 14-Day Post-Treatment Phone Contact
- Monitoring for adverse events

B. 4-Week Follow-up Assessment visit (21 to 60 days following study medication administration)
- Clinical assessment
- Monitoring for adverse events
- Clinical laboratory and microbiologic tests if indicated
- Clinical efficacy evaluation

The primary endpoint, clinical response at the 4-week follow-up assessment visit, was assessed by the investigator to be success of prophylaxis, failure of prophylaxis, or distant site infection. The Applicant discusses these responses extensively on pages 45-47 of the CSR. A brief description of each follows.

Success of Prophylaxis

Patients assessed as being a success of prophylaxis were required to meet all three of the following criteria:
- No signs or symptoms of infection at the surgical site.
- No further antimicrobial therapy was necessary.
- No surgical intervention for infection was necessary.

Failure of Prophylaxis

Patients assessed as being a failure of prophylaxis were classified as having development of a surgical site infection, receiving unexplained antibacterials, or experiencing an anastomotic leak. Patients who developed a surgical site infection were further classified as having a superficial incisional infection, a deep incisional infection, or an organ/space infection.

Distant Site Infection

Patients with a final clinical response of "distant site infection" were not evaluable for the primary analysis of efficacy. Distant site infections were documented as: urinary tract infection, pneumonia, vascular site, and "other" infections clearly unrelated to the surgical site. However, patients experiencing both a failure of prophylaxis and a distant site infection were considered to be a failure of prophylaxis for the primary endpoint. The total duration of systemic antibacterial therapy could not exceed the one-time dose of intravenous study therapy given 30-60 minutes prior to surgical incision.

If a patient developed a postoperative infection either at the surgical site or at a distant site, specimens were collected for aerobic and anaerobic culture. Two sets of blood cultures were obtained if a patient experienced a fever of >38.5ºC (101.2ºF) orally on 2 occasions at least 6 hours apart in a 24 hour period.

Medical Officer's comment: The definitions of success and failure of prophylaxis were generally acceptable.

6.1.3.3 Statistical Considerations

The co-primary efficacy analyses were performed using clinical outcomes at 4-weeks post-therapy (test-of-prophylaxis) in the clinically evaluable and MITT analysis sets. The clinically evaluable analysis set was a subset of the MITT set that satisfactorily completed the protocol (i.e., met inclusion and exclusion criteria, received adequate study therapy, and had appropriate follow-up). The MITT analysis set included all patients that met the minimal disease definition for elective colorectal surgery and received study therapy.

Additionally, the proportion of patients who 1) failed prophylaxis by reason for failure and 2) developed distant site infections overall and by type of infection were tabulated for each treatment group.

According to the Applicant, noninferiority of ertapenem to cefotetan was determined if the lower bound of the two-sided 95% confidence interval (CI) of the difference in the proportion of satisfactory clinical outcomes (ertapenem minus cefotetan) at the 4-week post-therapy follow-up assessment visit in the clinically evaluable analysis set was greater than -10%. The MITT population was expected to have a lower response rate than the clinically evaluable population, and the study was not powered to meet a noninferiority criterion of -10% in the MITT population.

On page 53 of the CSR, the Applicant stated that a test for superiority was performed after demonstrating non-inferiority (by the Applicant's analysis). Statistical superiority was defined by a 95% confidence interval for the difference in response rates (ertapenem minus cefotetan) with a lower limit greater than 0.

<u>Medical Officer's comment</u>: The Applicant initially proposed that non-inferiority between treatment arms could be declared if the lower bound of the 95% confidence interval (CI) was greater than -15%. In communications (fax, teleconference) between representatives of the Division and the Applicant, the Applicant was told that utilization of a delta of 15% might be problematic for approval if the data suggested that the lower bound of the 95% CI approached -15%. The Division agreed that it was not necessary for the MITT analysis to achieve the -10% criterion as long as this analysis was otherwise consistent with the efficacy analysis in the clinically evaluable population.

With regard to testing for statistical superiority, the Applicant acknowledged on page 53 of the CSR that, "Testing for superiority was not specified in the study protocol or data analysis plan." With regard to claiming clinical superiority, the Agency expects independent substantiation of clinical superiority, especially against a potential competitor, in a second adequate and well-controlled study. An in-depth discussion of the quality of data that the Agency would expect when reviewing a clinical superiority claim is presented in section 6.1.6.

On page 55 of the CSR, the Applicant stated that subgroup (exploratory) analyses were performed based on the type of surgical procedure, creatinine clearance, type of bowel

preparation, age, gender, and race to determine whether efficacy was consistent across different patient groups.

Determination of Sample Size
Using an alpha level = 0.025 (one-sided) and a response rate for each treatment group set at 80%, the Applicant determined that 340 clinically evaluable patients per group would provide 90% probability that the lower bound of the 95% (two-sided) confidence interval for the difference in the response rates would be greater than -10 percentage points.

6.1.3.4 Protocol Amendments and Changes in the Data Analysis Plan

There was one protocol amendment, 039-01. The Applicant states that the original protocol, 039-00, was never distributed to study sites. On page 56 of the CSR, the Applicant stated that all patients were enrolled under Protocol 039-01. The changes specified in Protocol 039-01 were not specified in the CSR. Therefore, Protocol 039-01 is the subject of this clinical review.

The Applicant made two minor amendments to the Data Analysis Plan (DAP). Originally, the Applicant stated that all pre-specified risk factors would be included in a multivariable risk factor analysis of surgical site infections. However, when performing the analysis, only significant risk factors (p-value < 0.3) from the univariate analysis were included. The second amendment to the DAP was the addition of a safety test. The proportion of patients with any serious drug-related clinical AEs was compared between treatment groups using risk difference.

Medical Officer's comments: The study design provided a reasonable assessment of benefit. The duration of the clinical study was adequate.

On page 37 of the CSR, under section 5.2, entitled, "Discussion of Study Design, Including the Choice of Control Groups," the Applicant stated that, "Both drugs were to be administered over a 30 minute period 30 to 60 minutes prior to surgery." On page 40 of the CSR, under section 5.4.1, "Treatments Administered," the Applicant stated, "Both drugs were to be given 30 to 60 minutes prior to the planned initial surgical incision as a single IV dose." The M.O. found similar statements on pages 1461 and 1464 of the Applicant's Data Analysis Plan. However, in the Efficacy Evaluability Document submitted with the CSR and found on pages 1449 to 1457, the Applicant stated on page 1453 that, "A patient must receive a complete dose of study therapy infused over 30 minutes within 2 hours prior to incision and within 6 hours of surgical closure to be considered evaluable."

The M.O. discusses this issue in further detail in sections 6.1.3.2, 6.1.4.3, and 6.1.6. Briefly, the prophylaxis response rates for the group of patients who received study therapy > 60 minutes up to 2 hours prior to surgical incision did not significantly differ from the prophylaxis response rates of the patients who received their study therapy within 60 minutes prior to skin incision. Therefore the M.O. did not contest this inconsistency in the study protocol.

Please refer to the original clinical review of NDA 21-337 for a detailed discussion of the adequacy of dose finding in Phase 2 as a basis for doses and dose regimens used in all the major effectiveness studies.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline Characteristics

One thousand and two patients were randomized into 1 of 2 treatment groups: 500 patients were assigned to the ertapenem group and 502 were assigned to the cefotetan group. Fifty patients were randomized but received no parenteral study therapy (24 to ertapenem and 26 to cefotetan); most commonly because of protocol deviations (surgical team gave a non-study antibiotic preoperatively or surgery was cancelled) or patients withdrew consent. Out of the remaining patients, 476 received ertapenem and 476 received cefotetan. On page 68, the Applicant states that the most common reason patients were excluded from the MITT population was that the minimal disease definition was not met. "This included 41 patients who did not undergo an appropriate colorectal surgery in addition to 49 of 50 patients randomized but not treated." Fifty-one sites in the United States enrolled patients. There were no foreign sites. No site enrolled more than 8.3% of the patients. Tables 4, 5, and 6 show the demographic characteristics of the treated population.

Table 4. Baseline Patient Characteristics by Treatment Group (Treated Population) (adapted from Applicant's Table 6-7, p 69)

	Ertapenem		**Cefotetan**		**Total**	
	(N=476)		**(N=476)**		**(N=952)**	
	n	(%)	n	(%)	n	(%)
Gender						
Female	204	(42.9)	213	(44.7)	417	(43.8)
Male	272	(57.1)	263	(55.3)	535	(56.2)
Race						
Asian	9	(1.9)	13	(2.7)	22	(2.3)
Black	49	(10.3)	62	(13.0)	111	(11.7)
Hispanic	41	(8.6)	36	(7.6)	77	(8.1)
White	377	(79.2)	362	(76.1)	739	(77.6)
Other	0	(0.0)	3	(0.6)	3	(0.3)
Age (Years)						
18 to 40	35	(7.4)	44	(9.2)	79	(8.3)
41 to 64	227	(47.7)	235	(49.4)	462	(48.5)
65 to 74	122	(25.6)	124	(26.1)	246	(25.8)
>74	92	(19.3)	73	(15.3)	165	(17.3)
Mean	61.6		60.3		60.9	
SD	13.96		13.93		13.96	
Median	63		61		62	
Range	23 to 92		21 to 94		21 to 94	

SD = Standard Deviation

Table 5. Summary of Surgical Procedures by Treatment Group (Treated Population) (modified from Applicant's Table 6-11, p 73-75)

	Ertapenem		**Cefotetan**		**Total**	
	(N=476)		**(N=476)**		**(N=952)**	
	n	(%)	n	(%)	n	(%)
Stratum						
Intraperitoneal	339	(71.2)	361	(75.8)	700	(73.5)
Abdominoperineal	132	(27.7)	111	(23.3)	243	(25.5)
Bowel Preparation						
No preparation	3	(0.6)	4	(0.8)	7	(0.7)
Polyethylene glycol solution	196	(41.2)	187	(39.3)	383	(40.2)
Polyethylene glycol solution with bisacodyl	18	(3.8)	16	(3.4)	34	(3.6)
Sodium phosphate solution	253	(53.2)	264	(55.5)	517	(54.3)
Not specified	1	(0.2)	1	(0.2)	2	(0.2)
Procedure						
Appendectomy	10	(2.1)	11	(2.3)	21	(2.2)
Biopsy liver	9	(1.9)	9	(1.9)	18	(1.9)
Cecectomy	8	(1.7)	13	(2.7)	21	(2.2)
Cholecystectomy	10	(2.1)	10	(2.1)	20	(2.1)
Colectomy	80	(16.8)	81	(17.0)	161	(16.9)
Colectomy partial	58	(12.2)	62	(13.0)	120	(12.6)
Hemicolectomy	137	(28.8)	150	(31.5)	287	(30.1)
Rectopexy	8	(1.7)	5	(1.1)	13	(1.4)
Resection of rectum	132	(27.7)	111	(23.3)	243	(25.5)
Salpingo-oophorectomy, bilateral	6	(1.3)	4	(0.8)	10	(1.1)
Sigmoidectomy	202	(42.4)	170	(35.7)	372	(39.1)
Small intestinal resection	5	(1.1)	2	(0.4)	7	(0.7)
Transverse colectomy	7	(1.5)	11	(2.3)	18	(1.9)
Other	69	(14.5)	61	(12.8)	130	(13.7)
Primary Diagnosis						
Benign colonic neoplasm	4	(0.8)	14	(2.9)	18	(1.9)
Bowel motility disorder	7	(1.5)	14	(2.9)	21	(2.2)
Colitis ulcerative	11	(2.3)	15	(3.2)	26	(2.7)
Colon adenoma	10	(2.1)	6	(1.3)	16	(1.7)
Colon cancer	217	(45.6)	206	(43.3)	423	(44.4)
Colonic polyp	18	(3.8)	23	(4.8)	41	(4.3)
Colonic stricture	0	(0.0)	6	(1.3)	6	(0.6)
Crohn's disease	7	(1.5)	2	(0.4)	9	(0.9)

Table 5. Summary of Surgical Procedures by Treatment Group (Treated Population) (cont'd) (modified from Applicant's Table 6-11, p 73-75)

	Ertapenem		Cefotetan		Total	
	(N=476)		(N=476)		(N=952)	
	n	(%)	n	(%)	n	(%)
Primary Diagnosis (cont'd)						
Diverticulitis intestinal	50	(10.5)	59	(12.4)	109	(11.4)
Familial adenomatous polyposis	2	(0.4)	5	(1.1)	7	(0.7)
Fistula	5	(1.1)	5	(1.1)	10	(1.1)
Rectal cancer	106	(22.3)	88	(18.5)	194	(20.4)
Rectal prolapse	14	(2.9)	8	(1.7)	22	(2.3)
Other	20	(4.2)	21	(4.4)	41	(4.3)
Duration of Surgery						
Duration ≤ 3.5 hours	393	(82.6)	397	(83.4)	790	(83.0)
Duration > 3.5 hours	78	(16.4)	75	(15.8)	153	(16.1)
Mean (SD) (min)	144.2 (72.3)		146.9 (75.1)		145.6 (73.7)	
N	471		472		943	
Median (min)	130.0		131.5		131.0	
Range (min)	15 to 434		9 to 518		9 to 518	
Time from Study Medication to Skin Incision						
Time ≤ 2 hours	453	(95.2)	444	(93.3)	897	(94.2)
Time > 2 hours	18	(3.8)	28	(5.9)	46	(4.8)
Mean (SD) (min)	61.8 (31.9)		62.4 (34.3)		62.1 (33.1)	
N	471		472		943	
Median (min)	58.0		56.0		57.0	
Range (min post-dosing to skin incision)	-242 to 215		-32 to 265		-242 to 265	

% = (n/Number of Patients Treated) x 100
SD = Standard Deviation
All procedures, primary diagnoses, and additional surgical findings with an incidence > 1% in either treatment are listed in the tables. All items with an incidence < 1% in bo h treatment groups were consolidated into the "other " category.
Patients could have multiple procedures, additional surgical findings, and procedure requirements.
The mean, median, and range for duration of surgery and time from study medica ion to skin incision are calculated in minutes.
Two (2) patients (AN 2188 and AN 2717) in the ertapenem group and two patients in the cefotetan group (AN 2272 and AN 2726) received study medication after skin incision. Therefore, the range of time from study medication to skin incision is shown as a negative number.
Four patients (AN 2005, AN 2098, AN 2710, AN 2968) in the ertapenem group and four patients (AN 2332, AN 2388, AN 2423, AN 3753) in the cefotetan group were treated but did not have surgery. One patient (AN 2522) in the ertapenem group had surgery performed but the surgical source documentation was lost. Baseline surgical information was not provided for these patients and they are not included in the summary.

Table 6. Risk Factors for Post-Operative Infection by Treatment Group (Treated Population) (adapted from Applicant's Table 6-15, p 82)

	Ertapenem		Cefotetan		Total	
	(N=476)		(N=476)		(N=952)	
	n	(%)	n	(%)	n	(%)
Tobacco Use						
Non-user	233	(48.9)	218	(45.8)	451	(47.4)
Current user	98	(20.6)	102	(21.4)	200	(21.0)
Ex-user	145	(30.5)	153	(32.1)	298	(31.3)
Not specified	0	(0.0)	3	(0.6)	3	(0.3)
BMI (kg/m^2)						
Mean (SD)	27.7	(5.9)	27.9	(6.2)	27.8	(6.0)
N	455		461		916	
Median	27		27.3		27.1	
Range	12.3 to 54.8		13.7 to 63.6		12.3 to 63.6	
Creatinine Clearance ($mL/min/1.73m^2$)						
> 30	451	(94.7)	451	(94.7)	902	(94.7)
≤ 30	5	(1.1)	8	(1.7)	13	(1.4)
Not specified	20	(4.2)	17	(3.6)	37	(3.9)
Obesity (BMI > 30 kg/m^2)						
	135	(28.4)	140	(29.4)	275	(28.9)
Diabetes						
	85	(17.9)	87	(18.3)	172	(18.1)
Albumin (Baseline Albumin ≤ 2 g/dL)						
	1	(0.2)	6	(1.3)	7	(0.7)

Creatinine Clearance calculation: Men=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL), Women=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL)*0.85
%=(n/Number of Patients Treated)*100
BMI was not calculated for 21 patients (ANs 2429, 2466, 2659, 2405, 2342, 2401, 2522, 2103, 2781, 2805, 2806, 2841, 2897, 2610, 2653, 2741, 2793, 2796, 2832, 3731, 3749) in the ertapenem group and 15 patients (ANs 2201, 2248, 2872, 2898, 2899, 2398, 2655, 2794, 2830, 2894, 2895, 3654, 3656, 3698, 2640) in the cefotetan group where height and/or weight were not provided.

Medical Officer's comment: In general, demographic characteristics in the treated population were evenly distributed between groups.

Tables 7, 8, and 9 summarize the baseline characteristics of the Evaluable Population according to the Applicant.

Table 7. Baseline Patient Characteristics by Treatment Group (Evaluable Population) (adapted from Applicant's Table 6-8, p 70)

	Ertapenem		**Cefotetan**		**Total**	
	(N=338)		**(N=334)**		**(N=672)**	
	n	(%)	n	(%)	n	(%)
Gender						
Female	148	(43.8)	158	(47.3)	306	(45.5)
Male	190	(56.2)	176	(52.7)	366	(54.5)
Race						
Asian	8	(2.4)	9	(2.7)	17	(2.5)
Black	39	(11.5)	46	(13.8)	85	(12.6)
Hispanic	25	(7.4)	24	(7.2)	49	(7.3)
White	266	(78.7)	252	(75.4)	518	(77.1)
Other	0	(0.0)	3	(0.9)	3	(0.4)
Age (Years)						
18 to 40	23	(6.8)	34	(10.2)	57	(8.5)
41 to 64	168	(49.7)	156	(46.7)	324	(48.2)
65 to 74	87	(25.7)	92	(27.5)	179	(26.6)
>74	60	(17.8)	52	(15.6)	112	(16.7)
Mean	61.3		60.2		60.8	
SD	13.65		14.39		14.03	
Median	63		62		62	
Range	23 to 92		21 to 94		21 to 94	

SD = Standard Deviation

Table 8. Summary of Surgical Procedures by Treatment Group (Evaluable Population)
(modified from Applicant's Table 6-12, p 76-77)

	Ertapenem		Cefotetan		Total	
	(N=338)		(N=334)		(N=672)	
	n	(%)	n	(%)	n	(%)
Stratum						
Intraperitoneal	253	(74.9)	265	(79.3)	518	(77.1)
Abdominoperineal	85	(25.1)	69	(20.7)	154	(22.9)
Bowel Preparation						
No preparation	0	(0.0)	0	(0.0)	0	(0.0)
Polyethylene glycol solution	148	(43.8)	138	(41.3)	286	(42.6)
Polyethylene glycol solution with bisacodyl	11	(3.3)	6	(1.8)	17	(2.5)
Sodium phosphate solution	178	(52.7)	189	(56.6)	367	(54.6)
Not specified	1	(0.3)	1	(0.3)	2	(0.3)
Procedure						
Appendectomy	8	(2.4)	8	(2.4)	16	(2.4)
Biopsy liver	8	(2.4)	8	(2.4)	16	(2.4)
Cecectomy	4	(1.2)	13	(3.9)	17	(2.5)
Cholecystectomy	6	(1.8)	9	(2.7)	15	(2.2)
Colectomy	64	(18.9)	56	(16.8)	120	(17.9)
Colectomy partial	43	(12.7)	49	(14.7)	92	(13.7)
Hemicolectomy	97	(28.7)	112	(33.5)	209	(31.1)
Ileectomy	1	(0.3)	4	(1.2)	5	(0.7)
Rectopexy	5	(1.5)	5	(1.5)	10	(1.5)
Resection of rectum	85	(25.1)	69	(20.7)	154	(22.9)
Salpingo-oophorectomy, bilateral	5	(1.5)	3	(0.9)	8	(1.2)
Sigmoidectomy	151	(44.7)	115	(34.4)	266	(39.6)
Small intestinal resection	4	(1.2)	0	(0.0)	4	(0.6)
Transverse colectomy	5	(1.5)	8	(2.4)	13	(1.9)
Other	40	(11.8)	33	(9.9)	73	(10.9)
Primary Diagnosis						
Benign colonic neoplasm	4	(1.2)	12	(3.6)	16	(2.4)
Bowel motility disorder	5	(1.5)	12	(3.6)	17	(2.5)
Colitis ulcerative	6	(1.8)	11	(3.3)	17	(2.5)
Colon adenoma	8	(2.4)	4	(1.2)	12	(1.8)
Colon cancer	162	(47.9)	153	(45.8)	315	(46.9)
Colonic polyp	15	(4.4)	18	(5.4)	33	(4.9)
Colonic stricture	0	(0.0)	6	(1.8)	6	(0.9)

Table 8. Summary of Surgical Procedures by Treatment Group (Evaluable Population) (cont'd) (modified from Applicant's Table 6-12, p 76-77)

	Ertapenem		Cefotetan		Total	
	(N=338)		(N=334)		(N=672)	
	n	(%)	n	(%)	n	(%)
Primary Diagnosis (cont'd)						
Crohn's disease	4	(1.2)	2	(0.6)	6	(0.9)
Diverticulitis intestinal	38	(11.2)	37	(11.1)	75	(11.2)
Familial adenomatous polyposis	2	(0.6)	5	(1.5)	7	(1.0)
Fistula	4	(1.2)	3	(0.9)	7	(1.0)
Rectal cancer	69	(20.4)	47	(14.1)	116	(17.3)
Rectal prolapse	12	(3.6)	7	(2.1)	19	(2.8)
Other	9	(2.7)	17	(5.1)	26	(3.9)
Duration of Surgery						
Duration ≤ 3.5 hours	298	(88.2)	296	(88.6)	594	(88.4)
Duration > 3.5 hours	40	(11.8)	38	(11.4)	78	(11.6)
Mean (SD) (min)	133.3 (60.1)		132.8 (60.4)		133.1 (60.2)	
N	338		334		672	
Median (min)	123.0		122.5		123.0	
Range (min)	15 to 314		9 to 313		9 to 314	
Time from Study Medication to Skin Incision						
Mean (SD) (min)	59 (22.6)		56.7 (25.0)		57.9 (23.8)	
N	338		334		672	
Median (min)	57.0		54.0		55.5	
Range (min post-dosing to skin incision)	13 to 120		0 to 119		0 to 120	

% = (n/Number of Patients Treated) x 100
SD = Standard Deviation
All procedures, primary diagnoses, and additional surgical findings with an incidence > 1% in either treatment are listed in the tables. All items with an incidence < 1% in bo h treatment groups were consolidated into the "other " category.
Patients could have multiple procedures, additional surgical findings, and procedure requirements.
The mean, median, and range for duration of surgery and time from study medica ion to skin incision are calculated in minutes.

Table 9. Risk Factors for Post-Operative Infection by Treatment Group (Evaluable Population) (adapted from Applicant's Table 6-16, p 83)

	Ertapenem		Cefotetan		Total	
	(N=338)		(N=334)		(N=672)	
	n	(%)	n	(%)	n	(%)
Tobacco Use						
Non-user	164	(48.5)	152	(45.5)	316	(47.0)
Current user	69	(20.4)	68	(20.4)	137	(20.4)
Ex-user	105	(31.1)	112	(33.5)	217	(32.3)
Not specified	0	(0.0)	2	(0.6)	2	(0.3)
BMI (kg/m^2)						
Mean (SD)	27.9	(5.9)	28.0	(6.4)	28.0	(6.1)
N	326		324		650	
Median	26.9		27.1		27.1	
Range	17.2 to 54.8		13.7 to 63.6		13.7 to 63.6	
Creatinine Clearance ($mL/min/1.73m^2$)						
> 30	321	(95.0)	319	(95.5)	640	(95.2)
≤ 30	4	(1.2)	5	(1.5)	9	(1.3)
Not specified	13	(3.8)	10	(3.0)	23	(3.4)
Obesity (BMI > 30 kg/m^2)						
	103	(30.5)	92	(27.5)	195	(29.0)
Diabetes						
	59	(17.5)	59	(17.7)	118	(17.6)
Albumin (Baseline Albumin ≤ 2 g/dL)						
	0	(0.0)	5	(1.5)	5	(0.7)

Creatinine Clearance calculation: Men=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL), Women=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL)*0.85

%=(n/Number of Patients Treated)*100

BMI was not calculated for 12 patients (ANs 2466, 2659, 2405, 2103, 2805, 2841, 2897, 2610, 2653, 2741, 2796, 3731) in the ertapenem group and 10 patients (ANs 2201, 2248, 2899, 2398, 2655, 2830, 2894, 2895, 3656, 2640) in the cefotetan group where height and/or weight were not provided.

Tables 10, 11, and 12 summarize the baseline characteristics of the Evaluable Population according to the Medical Officer. Statistical support provided by Yunfan Deng, Ph.D., Biostatistics Reviewer.

Table 10. Baseline Patient Characteristics by Treatment Group (Evaluable Population According to Medical Officer)

	Ertapenem		Cefotetan		Total	
	(N=346)		(N=339)		(N=685)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	153	(43.8)	160	(47.3)	313	(45.6)
Male	193	(56.2)	179	(52.7)	372	(54.4)
Race						
Asian	8	(2.3)	9	(2.7)	17	(2.5)
Black	40	(11.6)	46	(13.6)	86	(12.6)
Hispanic	26	(7.5)	24	(7.1)	50	(7.3)
White	272	(78.6)	257	(75.8)	529	(77.2)
Other	0	(0.0)	3	(0.9)	3	(0.4)
Age (Years)						
18 to 40	24	(6.9)	36	(10.6)	60	(8.8)
41 to 64	171	(49.4)	158	(46.6)	329	(48.0)
65 to 74	89	(25.7)	93	(27.4)	182	(26.6)
>74	62	(17.9)	52	(15.4)	114	(16.6)
Mean	61.3		60.0		60.7	
SD	13.68		14.43		14.06	
Median	63		62		62	
Range	23 to 92		21 to 94		21 to 94	

SD = Standard Deviation

Table 11. Summary of Surgical Procedure by Treatment Group (Evaluable Population According to Medical Officer)

	Ertapenem		Cefotetan		Total	
	(N=346)		(N=339)		(N=685)	
	n	(%)	n	(%)	n	(%)
Stratum						
Intraperitoneal	259	(74.9)	270	(79.6)	529	(77.2)
Abdominoperineal	87	(25.1)	69	(20.4)	156	(22.8)
Bowel Preparation						
No preparation	0	(0.0)	0	(0.0)	0	(0.0)
Polyethylene glycol solution	149	(43.1)	141	(41.6)	290	(42.3)
Polyethylene glycol solution with bisacodyl	12	(3.5)	6	(1.8)	18	(2.6)
Sodium phosphate solution	184	(53.2)	191	(56.3)	375	(54.7)
Not specified	1	(0.3)	1	(0.3)	2	(0.3)
Procedure						
Appendectomy	8	(2.3)	8	(2.4)	16	(2.3)
Biopsy liver	8	(2.3)	8	(2.4)	16	(2.3)
Caecectomy	4	(1.2)	13	(3.8)	17	(2.5)
Cholecystectomy	6	(1.7)	9	(2.7)	15	(2.2)
Colectomy	65	(18.9)	58	(17.1)	123	(18.0)
Colectomy partial	44	(12.7)	49	(14.5)	93	(13.6)
Hemicolectomy	100	(28.9)	113	(33.3)	213	(31.1)
Ileectomy	1	(0.3)	4	(1.2)	5	(0.7)
Rectopexy	5	(1.4)	5	(1.5)	10	(1.5)
Resection of rectum	87	(25.1)	69	(20.4)	156	(22.8)
Salpingo-oophorectomy, bilateral	5	(1.4)	3	(0.9)	8	(1.2)
Sigmoidectomy	154	(44.5)	119	(35.1)	273	(39.9)
Small intestinal resection	4	(1.2)	0	(0.0)	4	(0.6)
Transverse colectomy	5	(1.4)	8	(2.4)	13	(1.9)
Other	40	(11.6)	35	(10.3)	75	(10.9)
Primary Diagnosis						
Benign colonic neoplasm	4	(1.2)	12	(3.5)	16	(2.3)
Bowel motility disorder	5	(1.5)	13	(3.8)	18	(2.6)
Colitis ulcerative	7	(2.0)	11	(3.2)	18	(2.6)
Colon adenoma	8	(2.3)	4	(1.2)	12	(1.8)
Colon cancer	164	(47.4)	155	(45.7)	319	(46.6)
Colonic polyp	16	(4.6)	18	(5.3)	34	(5.0)
Colonic stricture	0	(0.0)	6	(1.8)	6	(0.9)

Table 11. Summary of Surgical Procedure by Treatment Group (Evaluable Population According to Medical Officer) (cont'd)						
	Ertapenem		**Cefotetan**		**Total**	
	(N=346)		**(N=339)**		**(N=685)**	
	n	(%)	n	(%)	n	(%)
Primary Diagnosis (cont'd)						
Crohn's disease	4	(1.2)	2	(0.6)	6	(0.9)
Diverticulitis intestinal	39	(11.3)	38	(11.2)	77	(11.2)
Familial adenomatous polyposis	2	(0.6)	5	(1.5)	7	(1.0)
Fistula	4	(1.2)	4	(1.2)	8	(1.2)
Rectal cancer	71	(20.5)	47	(13.9)	118	(17.2)
Rectal prolapse	12	(3.5)	7	(2.1)	19	(2.8)
Other	10	(2.9)	17	(5.0)	27	(3.9)
Duration of Surgery						
Duration $\leq$ 3.5 hours	304	(87.9)	300	(88.5)	604	(88.2)
Duration > 3.5 hours	42	(12.1)	39	(11.5)	81	(11.8)
Mean (SD) (min)	133.4 (60.5)		133.6 (60.8)		133.5 (60.6)	
N	346		339		685	
Median (min)	123.0		124		123.0	
Range (min)	15 to 314		9 to 313		9 to 314	
Time from Study Medication to Skin Incision						
Mean (SD) (min)	58.9 (22.5)		56.7 (24.8)		57.8 (23.7)	
N	346		339		685	
Median (min)	57.0		54.0		56	
Range (min post-dosing to skin incision)	13 to 120		0 to 119		0 to 120	

% = (n/Number of Patients Treated) x 100

SD = Standard Deviation
All procedures, primary diagnoses, and additional surgical findings with an incidence > 1% in either treatment are listed in the tables. All items with an incidence < 1% in bo h treatment groups were consolidated into the "other" category.

Patients could have multiple procedures, additional surgical findings, and procedure requirements.
The mean, median, and range for duration of surgery and time from study medica ion to skin incision are calculated in minutes.

Table 12. Risk Factors for Post-Operative Infection by Treatment Group (Evaluable Population According to Medical Officer)

	Ertapenem		Cefotetan		Total	
	(N=346)		(N=339)		(N=685)	
	n	(%)	n	(%)	n	(%)
Tobacco Use						
Non-user	168	(48.6)	154	(45.4)	322	(47.0)
Current user	70	(20.2)	69	(20.4)	139	(20.3)
Ex-user	108	(31.2)	114	(33.6)	222	(32.4)
Not specified	0	(0.0)	2	(0.6)	2	(0.3)
BMI (kg/m^2)						
Mean (SD)	28.0	(5.9)	28.1	(6.4)	28.0	(6.1)
N	334		329		663	
Median	27.0		27.1		27.1	
Range	17.0 to 54.8		13.7 to 63.6		13.7 to 63.6	
Creatinine Clearance ($mL/min/1.73m^2$)						
> 30	329	(95.0)	324	(95.5)	653	(95.3)
≤ 30	4	(1.2)	5	(1.5)	9	(1.3)
Not specified	13	(3.8)	10	(3.0)	23	(3.4)
Obesity (BMI > 30 kg/m^2)						
	106	(30.6)	94	(27.7)	200	(29.2)
Diabetes						
	62	(17.9)	60	(17.7)	122	(17.8)
Albumin (Baseline Albumin ≤ 2 g/dL)						
	0	(0.0)	5	(1.5)	5	(0.7)

Creatinine Clearance calculation: Men=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL), Women=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL)*0.85

%=(n/Number of Patients Treated)*100

BMI was not calculated for 12 patients (ANs 2466, 2659, 2405, 2103, 2805, 2841, 2897, 2610, 2653, 2741, 2796, 3731) in the ertapenem group and 10 patients (ANs 2201, 2248, 2899, 2398, 2655, 2830, 2894, 2895, 3656, 2640) in the cefotetan group where height and/or weight were not provided.

Medical Officer's comment: In general, demographic characteristics in the Applicant's and Medical Officer's Evaluable populations were similar. Characteristics were evenly distributed between groups, including stratum of surgery, as well as other potential risk factors for postoperative infection.

6.1.4.2 Evaluability

Table 13 summarizes the Applicant's determinations of the MITT evaluable set based on information found in Table 6-6 on page 68 of the CSR. One-hundred one randomized patients were not MITT evaluable: 49 (9.8%) randomized to the ertapenem group and 52 (10.4%) randomized to the cefotetan group. The most common reason patients were excluded from the MITT population was that the minimal surgical definition was not met. This included 41

patients who did not undergo an appropriate colorectal surgery in addition to 49 of the 50 patients randomized but not treated. Twenty-four (24) patients in the ertapenem group and 26 patients in the cefotetan group were randomized but did not receive study medication and were excluded from the MITT population. One patient in the cefotetan group received only a partial dose of study medication and was excluded from the MITT population.

Table 13. Applicant's Accounting of MITT Evaluability (adapted from Applicant's Table 6-6, p 68)

Population and Reasons Not MITT Evaluable	**Ertapenem**		**Cefotetan**		**Total**	
Randomized population	**(N=500)**		**(N=502)**		**(N=1002)**	
	n	(%)	n	(%)	n	(%)
MITT Population						
MITT evaluable	451	(90.2)	450	(89.6)	901	(89.9)
MITT non-evaluable	49	(9.8)	52	(10.4)	101	(10.1)
Bowel preparation violation	3	(0.6)	5	(1.0)	8	(0.8)
Minimal surgical definition not met	45	(9.0)	45	(9.0)	90	(9.0)
Other	3	(0.6)	2	(0.4)	5	(0.5)
Study therapy violation	24	(4.8)	27	(5.4)	51	(5.1)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being non-MITT evaluable, the patient will be counted only once in the non-MITT evaluable category.

MITT=modified-intent-to-treat

% = (n / Number of Patients Randomized) x 100

Medical Officer's comment: The M.O. concurred with the Applicant's determinations of MITT evaluability.

Table 14 summarizes the Applicant's determinations of the Clinically Evaluable (Evaluable) set based on information found in Table 6-5 on page 67 of the CSR. The most common reason why patients were not considered evaluable was study therapy violation. Ninety (90) patients were deemed nonevaluable because of a study therapy violation. Thirty-four (34) patients received study medication > 2 hours before surgical incision, 38 patients received study medication > 6 hours before surgical closure, and 12 patients received study medication > 2 hours before incision and > 6 hours before closure. Other major reasons why patients were considered nonevaluable were: (1) distant site infection with concomitant antibiotic administration (and no evidence of subsequent wound infection), prior/concomitant antibiotic administration, and minimal surgical definition not met.

Table 14. Applicant's Accounting of Evaluability (Treated Population) (adapted from Applicant's Table 6-5, p 67 of CSR)

Population and Reasons Not Evaluable	Ertapenem		Cefotetan		Total	
No. subjects treated with study drug	**(N=476)**		**(N=476)**		**(N=952)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Evaluable population	**338**	**(71.0)**	**334**	**(70.2)**	**672**	**(70.6)**
Non-evaluable at 4-Week Follow-up visit	138	(29.0)	142	(29.8)	280	(29.4)
4-week follow-up window violation	4	(1.4)	8	(2.8)	8	(2.8)
Baseline/intercurrent medical event	2	(0.7)	4	(1.4)	4	(1.4)
Bowel preparation violation	2	(0.7)	2	(0.7)	2	(0.7)
Distant site infection with concomitant antibiotic administration and no evidence of subsequent wound infection	28	(9.7)	24	(8.4)	24	(8.4)
Minimal surgical definition not met	16	(5.5)	21	(7.3)	21	(7.3)
No 4-week follow-up (other than prior failure)	0	(0.0)	2	(0.7)	2	(0.7)
Other	28	(9.7)	29	(10.1)	29	(10.1)
Prior/Concomitant antibiotics violation	32	(11.1)	41	(14.3)	41	(14.3)
Other	0	(0.0)	1	(0.3)	1	(0.3)
Study therapy violation	5	(1.7)	9	(3.1)	9	(3.1)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being non-evaluable, the patient will be counted only once in the non-evaluable category.

%=(n/Number of Patients Treated) x 100

<u>Medical Officer's comments</u>: This Medical Officer performed a blinded review of a random sample of 15% of the case report forms (CRFs) from this trial to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with the Applicant's evaluability and outcome determinations. Based on the M.O.'s blinded, random sample review and the subsequent review of over 140 additional CRFs, the M.O. has made the following changes to the Applicant's evaluable populations:

- ***13 patients (8 in the ertapenem group and 5 in the cefotetan group) were changed from clinically nonevaluable to clinically evaluable***

In this Medical Officer's analysis, the reasons patients were changed from clinically nonevaluable to evaluable were as follows. Nine patients initially deemed to be nonevaluable due to a "prior or concomitant antibiotic violation" were found not to have such a violation and therefore made clinically evaluable (Patients 2858, 2859, 2233, 2636, 2947, 2481, 2853, 2473, and 2701). Two patients initially deemed by the Applicant to be nonevaluable due to a "4-week follow-up violation" were found not to have this violation and therefore made clinically evaluable (Patients 2624 and 2875). Two patients initially deemed to be nonevaluable due to a "study therapy violation" were found not to have this violation and were made clinically evaluable (Patients 2130 and 2131). Applicant agreement with these evaluability changes was documented in Merck's February 17, 2006 Response to the FDA Information Request of January 6, 2006.

The following figure displays the M.O.'s profile for study enrollment and summarizes the number of patients in each of the evaluable study therapy populations according to the M.O. The changes made have resulted in a net increase of 8 evaluable patients in the ertapenem group and a net increase of 5 evaluable patients in the cefotetan group.

The following Figure 1, entitled, "Medical Officer's Profile of Patient Enrollment" is adapted from a similar figure created by the Applicant, Figure 6-1 on page 102 of CSR.

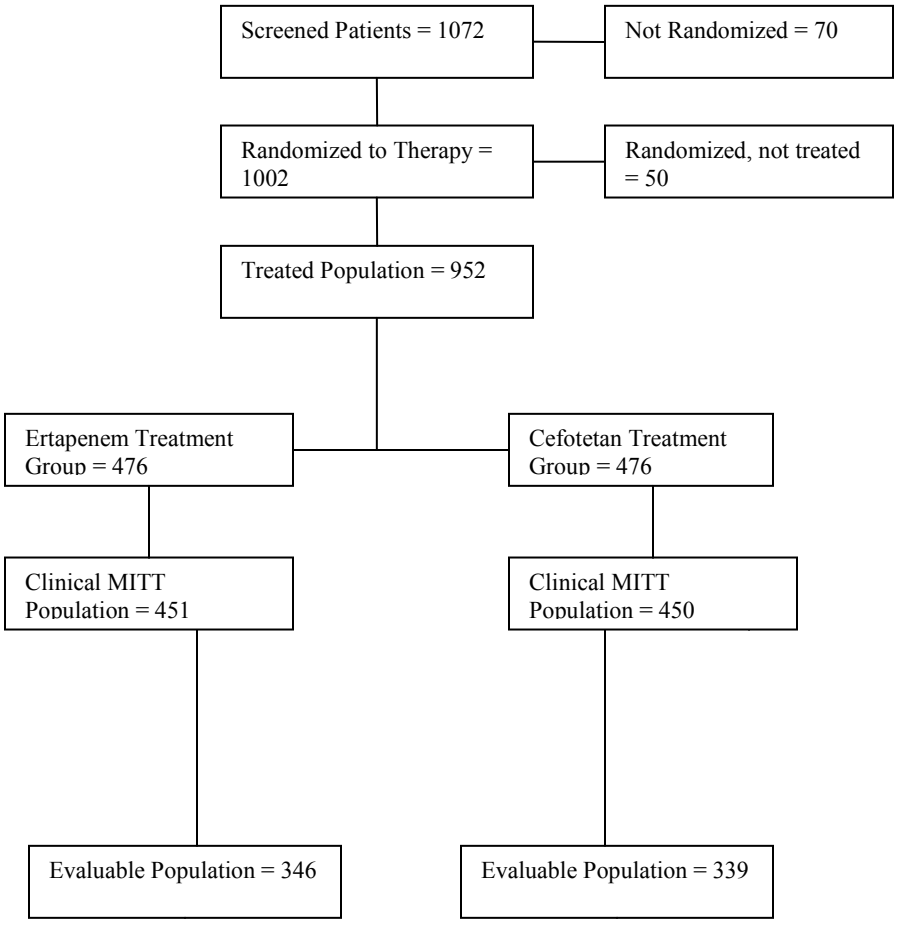


Figure 1. Medical Officer's Profile of Patient Enrollment

<u>Medical Officer's comments</u>: Based on the M.O.'s blinded review of CRFs, on a case-by-case basis, the M.O. identified several discrepancies between the Applicant's actual determination of patient evaluability and the criteria published in the Applicant's Data Analysis Plan (DAP). The M.O. communicated these discrepancies to the Applicant in an FDA Request for Additional Information on January 6, 2006. The Applicant responded on February 17, 2006. Based on these issues and feedback from the Applicant, the Medical Officer's final determinations of patient evaluability are summarized below.

1. ***The Applicant considered the following patients nonevaluable for the per protocol analysis due to prior or concomitant antibiotic violations: 2858, 2859, 2233, 2636, 2947, 2481, and 2853. However, on further review of the following sections of the Clinical Study Report (CSR): section 5.5.3.1 "Success of Prophylaxis" on page 45, section 5.5.3.2 "Unexplained antibiotic use" on page 47, section 5.4.6 "Prior and Concomitant Therapy" on page 43, and section 5.3.2 Exclusion criteria "i" on page 39, the Applicant concurred with the M.O. that these patients were indeed evaluable, and identified two additional patients (Patients 2473 and 2701) who were also reassigned to the evaluable set due to this issue.***

2. ***The Applicant considered the following patients nonevaluable for the per protocol analysis due to a 4-week follow-up window violation: 2624 and 2875. However, based on the section titled "Evaluable Patients at the 4-Week Posttreatment Follow-Up Assessment on page 1451 of the CSR, it appeared that the previously listed patients were evaluable. Specifically, Patient 2624 had surgery on 3/11/04 and was deemed a failure by the investigator on 4/9/04. The patient was noted to have wound dehiscence and received antibiotics (keflex 4/9-4/11/04 and amoxicillin 4/21/04-5/1/04) for an abdominal fluid collection. Therefore, according to page 1451, the failure should carry forward. Patient 2875 had a 4-week follow-up visit within the 60-day limit noted on page 1451 of the CSR. The Applicant concurred with the M.O. that these patients were indeed evaluable.***

3. ***Originally, the Applicant considered Patient 2131 nonevaluable due to a study therapy violation. However, upon further query by the M.O. regarding the nature of the study therapy violation, the Applicant investigated and found that Patient 2131 had "received a complete dose of study therapy infused within 2 hours prior to incision and within 6 hours of surgical closure." Patient 2131's evaluability was changed to "evaluable." Additionally, the Applicant identified that Patient 2130 should also be reassigned to the evaluable set due to this issue.***

6.1.4.3 Results

Clinical Outcomes

The primary endpoint for this trial was clinical outcome at the 4-week follow-up assessment visit 21-60 days after study therapy administration; analyses of the Clinically Evaluable (Evaluable) and modified intent-to-treat (MITT) populations were considered co-primary. Table 15 shows the proportions of patients with satisfactory clinical outcomes at the 4-week follow-up assessment adjusted for surgical procedure. In the Applicant's original analysis of clinically evaluable patients, favorable clinical response rates were 72.0% for ertapenem and 57.2% for cefotetan. On January 6, 2006, the Medical Officer provided a list of changes in patient evaluability based on a blinded review of 15% of case report forms (CRFs) and targeted review of over 140 additional CRFs. On February 17, 2006, the Applicant provided concurrence with the Medical Officer's evaluability changes and revised their efficacy analyses. The Applicant's

revised analysis concurs with the Medical Officer's analysis with response rates of 70.6% for ertapenem and 57.3% for cefotetan. For patients in the MITT set, favorable clinical response rates adjusted for surgical procedure were 58.4% for ertapenem and 48.8% for cefotetan in both the Applicant's and Medical Officer's analyses. The observed favorable clinical response rates in the MITT set were 58.3% for ertapenem and 48.9 for cefotetan in both the Applicant's and Medical Officer's analyses. For all analyses, the lower limits of the 95% CIs around the treatment differences were greater than -10%.

Table 15. Adjusted Clinical Outcomes at Follow-up (Evaluable and MITT)

	Ertapenem (A)				Cefotetan (B)					
	Estimated¥ Response				Estimated¥ Response				Estimated¥ Difference (A - B)	
Analysis Set	N	n	%	(95% CI)	N	n	%	(95% CI)	%	(95% CI)
Evaluable										
Applicant	338	243	72.0	(67.2, 76.8)	334	191	57.2	(51.9, 62.6)	14.8	(7.5, 21.9)
Medical Officer	346	244	70.6	(65.8, 75.4)	339	194	57.3	(52.0, 62.6)	13.3	(6.1, 20.4)
MITT										
Applicant	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)
Medical Officer	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)

¥ Computed from a statistical model adjusting for surgical procedure.

N = Number of Evaluable patients in each treatment group.

n = Number of Evaluable patients with a favorable clinical response each treatment group.

CI = Confidence interval.

Applicant's results for Evaluable and MITT from Tables 7-1 (p. 99) of the CSR and the 4/27/06 Information Amendment, respectively.

Medical Officer's comment: The evaluability changes in the Medical Officer's analysis set do not affect the overall study results. Additionally, the M.O. did not identify any discrepancies between the Applicant's actual determination of patient outcome and the criteria published in the Applicant's Data Analysis Plan (DAP). These analyses support the conclusion that ertapenem is noninferior to cefotetan for prophylaxis against surgical site infection in elective colorectal surgery patients. The observed analyses for the clinically evaluable (Evaluable) and MITT populations follow in Tables 16 and 17. The results were not substantially different from the analyses adjusted for surgical procedure. Because there were no significant differences between the prophylaxis rates in the observed and adjusted analyses, and for the sake of clarity of derivation of numbers, the observed results are reported in the label.

Table 16 provides the Applicant's February 17, 2006 revised observed clinical outcomes at the 4-week follow-up assessment stratified by surgical procedure in the Clinically Evaluable set. These results concur with the Medical Officer's analysis.

Table 16. Applicant's Revised Observed Clinical Outcomes at Follow-up Stratified by Surgical Procedure (Evaluable)

	Ertapenem (A) (N=346) Observed¥ Response			Cefotetan (B) (N=339) Observed¥ Response			Observed¥ Differences (A-B)	
Surgical Procedure	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Evaluable								
Intraperitoneal	185/259	71.4	(65.5, 76.8)	153/270	56.7	(50.5, 62.7)	14.8	(6.6, 22.7)
Abdominoperineal	59/87	67.8	(56.9, 77.4)	41/69	59.4	(46.9, 71.1)	8.4	(-6.7, 23.5)
Overall	244/346	70.5	(65.4, 75.3)	194/339	57.2	(51.8, 62.6)	13.3	(6.1, 20.4)

¥ For overall, computed from a statistical model adjusting for surgical procedure.

N = Number of evaluable patients in each treatment group.

n/m = Number of evaluable patients with a favorable clinical assessment / number of Evaluable patients with assessment.
CI = Confidence interval.

Applicant's results from Table 3 of February 17, 2006 Response to FDA Request of January 6, 2006.

Table 17 provides the Applicant's observed clinical outcomes for the MITT analysis set. The point estimates for observed response and observed difference concur with those found in the FDA's analysis. Statistical support provided by Yunfan Deng, Ph.D., Biostatistics Reviewer.

Table 17. Observed Clinical Outcomes at Follow-up (MITT)

	Ertapenem (A) Observed Response				Cefotetan (B) Observed Response				Observed Difference (A - B)	
Analysis Set	N	n	%	(95% CI)	N	n	%	(95% CI)	%	(95% CI)
MITT										
Applicant	451	263	58.3	(53.8, 62.9)	450	220	48.9	(44.3, 53.5)	9.4	(2.9, 15.9)
FDA	451	263	58.3	(53.6, 62.9)	450	220	48.9	(44.2, 53.6)	9.4	(2.9, 15.9)

N = Number of evaluable patients in each treatment group.

n = Number of evaluable patients with a favorable clinical response each treatment group.

CI = Confidence interval.

Applicant's results from Table 7-28 of May 11, 2006 Response to FDA request of May 2, 2006.

Medical Officer's comments: ***This single adequate and well-controlled clinical study demonstrates that ertapenem is non-inferior to cefotetan for prophylaxis against surgical site infection in elective colorectal surgery patients. A single study is sufficient to demonstrate non-inferiority in this particular case because the Applicant can draw upon the clinical experience used to demonstrate that ertapenem was noninferior to comparators in both complicated intra-abdominal infections and complicated skin and skin structure infections.***

(b) (4)

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(b) (4)

A second issue that the M.O. noted during the review of Study 039 was that the prophylaxis success rate in the cefotetan arm (52.7%) was significantly lower than in previous studies of prophylaxis against surgical site infections in elective colorectal surgery patients. The M.O. noted that in a multicenter study of alatrofloxacin versus cefotetan by Milsom et al. (1998), both study arms had prophylaxis success rates of 72% in elective colorectal surgery patients.[3] The M.O. asked the Applicant to provide an explanation why the cefotetan prophylaxis success rate in the Study 039 was substantially lower than that observed in the most recent prior clinical trial of prophylaxis of surgical site infection in elective colorectal surgery patients using cefotetan as the comparator agent.

The Applicant responded on April 6, 2006 and stated the following with regard to the study by Milsom et al.

> "While the rate of prophylaxis failure among patients treated with cefotetan as reported by the Milsom paper is still lower than that seen in our cefotetan group (42.8%), the inclusion criteria are not identical. The third most prevalent procedure in the Milsom study, ostomy takedown, was excluded from our study. This procedure accounted for 14.2% (30/212) of all procedures (third most common) in patients in the Milsom cefotetan group. Ostomy takedown has been associated with a substantially lower rate of surgical site infection compared to other common colorectal procedures, and this is confirmed in the Milsom study; only 13.3% of patients in the cefotetan group who underwent ostomy takedown experienced prophylaxis failure. This compares to a 33% (21/63) prophylaxis failure rate in cefotetan patients who underwent hemicolectomy, the most common procedure in the Milsom cefotetan group."

The M.O. notes that while the inclusion of ostomy takedown procedures may account for a portion of the prophylaxis success rate in the cefotetan arm of the Milsom study, removal of such patients from the Milsom study results in an overall success rate of 69.8% (127/182) and therefore does not completely explain the lower prophylaxis response rate of 57.2% observed in Study 039.

In the April 6, 2006 response, the Applicant provided additional reasons for why the Study 039 prophylactic success rate may have been lower than historical controls. These reasons included increased prevalence of obesity among patients enrolled in Study 039 and varied definitions for the primary endpoint in other studies published between 1988 and 1992.[4,5,6,7] Beyond these possible explanations, the Applicant stated, "…the Sponsor cannot provide an exact explanation as to why the response for the comparator is different in this study."

Table 18 provides the Applicant's February 17, 2006 revised analysis of reasons for failed prophylaxis at the 4-week follow-up visit. These results concur with the Medical Officer's analysis.

Table 18. Revised Reasons for Failed Prophylaxis at 4-Week Follow-up (Evaluable)

	Ertapenem (A) (N=346)			Cefotetan (B) (N=339)			Estimated[¥] Differences (A-B)	
	Estimated[¥] Response			Estimated[¥] Response				
Reason for Failure	n	%	(95% CI)	n	%	(95% CI)	%	(95% CI)
Any Failure	**102**	**29.4**	**(24.6, 34.2)**	**145**	**42.7**	**(37.4, 48.0)**	**-13.3**	**(-20.4, -6.1)**
Surgical Site Infection	63	17.9	(13.9, 22.0)	105	30.9	(26.0, 35.9)	-13.0	(-19.4, -6.6)
Organ/Space	5	1.5	(0.2, 2.7)	12	3.6	(1.6, 5.6)	-2.1	(-4.9, -0.2)
Deep Incisional	13	3.6	(1.6, 5.7)	17	5.0	(2.7, 7.3)	-1.3	(-4.6, 1.8)
Superficial Incisional	45	12.8	(9.3, 16.4)	76	22.3	(17.9, 26.8)	-9.5	(-15.2, -3.8)
Unexplained Antibiotic Use	29	8.5	(5.6, 11.4)	26	7.7	(4.9, 10.5)	0.8	(-3.4, 5.0)
Anastomotic Leak	10	3.0	(1.2, 4.7)	14	4.1	(2.0, 6.2)	-1.1	(-4.2, 1.7)

[¥] Percents and 95% Confidence Intervals computed from a statistical model adjusting for surgical procedure.

N = Number of evaluable patients in each treatment group.

n = Number of evaluable patients within failure category.

CI = Confidence interval.

Applicant's results from Table 4 of February 17, 2006 Response to FDA Request of January 6, 2006. The 3 major categories of failure of prophylaxis are highlighted.

Secondary efficacy endpoints included the following. (1) The proportion of patients with a distant site infection any time up to the 4-week post-treatment visit (see Table 19). (2) The proportion of patients who developed the presence of microbiologic pathogens (any pathogen and for each pathogen) (see Tables 20 and 21).

Medical Officer's comment: The results of these secondary efficacy endpoint analyses are consistent with those of the primary endpoint analyses. Please see the following for further details.

Table 19 describes the types of distant site infections observed in the study.

Table 19. Proportion of Patient's with Distant Site Infections at 4-Weeks Post-Treatment by Type of Infection (MITT Population)

	Ertapenem (A) (N=451)			Cefotetan (B) (N=450)			Estimated¥ Differences (A-B)	
	Estimated¥ Response			Estimated¥ Response				
Distant Site Infection	n	%	(95% CI)	n	%	(95% CI)	%	(95% CI)
Any Distant Site Infection	**48**	**10.6**	**(7.8, 13.5)**	**55**	**12.3**	**(9.3, 15.4)**	**-1.7**	**(-5.9, 2.5)**
Pneumonia	13	2.8	(1.3, 4.4)	23	5.0	(3.0, 7.0)	-2.2	(-4.9, 0.4)
Urinary Tract Infection	20	4.4	(2.5, 6.3)	29	6.4	(4.2, 8.7)	-2.1	(-5.1, 0.9)
Vascular Site Infection	1	0.2	--	0	0	--	0.2	--
Other	18	4.0	(2.2, 5.7)	12	2.6	(1.1, 4.1)	1.4	(-1.0, 3.9)

¥ Percents and 95% Confidence Intervals computed from a statistical model adjusting for surgical procedure.

Patients could have developed multiple distant site infections. Although a patient may have more than one distant site infection they are counted once in the "Any Distant Site Infection" category.
N = Number of MITT qualified patients in each treatment group.

n = Number of patients with a specific distant site infection.

CI = Confidence interval.

Adapted from Applicant's Table 7-17 of CSR, p 148.

Microbiologic outcomes

One hundred twenty-four (124) pathogens were isolated from 30 patients in the ertapenem group and 152 pathogens were isolated from 56 patients in the cefotetan group. On page 102 of the CSR, the Applicant states that the most frequently isolated pathogens were gram positive aerobic cocci with Enterococcus, *Enterococcus faecalis*, and *Staphylococcus aureus* as the predominate species identified. Gram negative anaerobic coccobacilli were also isolated with *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* being the most frequently observed. Gram negative aerobic bacilli were isolated in fewer numbers with *Escherichia coli* and *Pseudomonas aeruginosa* most frequently identified. Gram positive anaerobic bacilli were isolated but no organisms were frequently seen with the exception of *Clostridium innocuum* and *Eubacterium lentum* in the cefotetan group.

Medical Officer's comment: ***Due to changes in evaluability, the M.O. added surgical site infection culture data from one additional failure to the list of documented pathogens, cefotetan patient (Patient-site) 2481-041. Patient 2481-041 reportedly had a "Superficial Incisional Infection." The culture was a "wound curettage" of "abdominal cavity drainage," and the pathogen was identified as Bacteroides uniformis. The M.O.'s change is reflected in the following Table 20, but not in Table 21. None of the other 8 failures who were changed from nonevaluable to evaluable had culture data from the surgical site.***

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Table 20. Documented Pathogens with an Incidence > 1% from the Surgical Site* by Treatment Group (Evaluable Population) (modified from Applicant Table 7-4 on pages 103-105 of CSR)

All Documented Pathogens	Ertapenem (N=346)		Cefotetan (N=339)	
	n=30		n=56	
	124		152	
	m	(%)	m	(%)
gram-positive aerobic cocci	**42**	**33.9**	**51**	**33.6**
Enterococcus	8	6.5	11	7.2
Enterococcus faecalis	4	3.2	10	6.6
Enterococcus faecium	1	0.8	3	2.0
Staphylococcus	4	3.2	3	2.0
Staphylococcus aureus	9	7.3	10	6.6
MRSA	2	1.6	2	1.3
MSSA	4	3.2	3	2.0
methicillin-sensitivity not specified	3	2.4	5	3.3
Streptococcus	4	3.2	3	2.0
Streptococcus agalactiae	1	0.8	4	2.6
Streptococcus milleri	2	1.6	0	0.0
Streptococcus viridans	3	2.4	3	2.0
gram-positive aerobic bacilli	**3**	**2.4**	**0**	**0.0**
Bacillus	2	1.6	0	0.0
gram-negative aerobic bacilli	**17**	**13.7**	**23**	**15.1**
Enterobacter aerogenes	0	0.0	2	1.3
Escherichia coli	7	5.6	7	4.6
Klebsiella pneumoniae	1	0.8	2	1.3
Morganella morganii	0	0.0	2	1.3
Proteus mirabilis	3	2.4	1	0.7
Pseudomonas aeruginosa	3	2.4	7	4.6
gram-positive anaerobic cocci	**5**	**4.0**	**4**	**2.6**
Peptostreptococcus anaerobius	0	0.0	2	1.3
Peptostreptococcus magnus	2	1.6	1	0.7
Peptostreptococcus micros	2	1.6	0	0.0

*Isolates obtained from surgical site infection or anastomotic leak failures.

The number of documented pa hogens by pa hogen is a count of documented pathogens across all pa ients/pathogens. This number may be greater than the number of patients due to the possibility of a patient having a documented pathogen for more than 1 pathogen/strain.

N=Number of evaluable patients in each treatment group.

n=Number of patients with a documented pathogen in each treatment group.

m=Number of documented pathogens.

%=Number of documented pathogens / all pa hogens

Documented Pathogens with an Incidence > 1% from the Surgical Site* by Treatment Group (Evaluable Population) (cont'd) (modified from Applicant Table 7-4 on pages 103-105 of CSR)

All Documented Pathogens	Ertapenem (N=346)		Cefotetan (N=339)	
	n=30		n=56	
	124		152	
	m	(%)	m	(%)
gram-positive anaerobic bacilli	**20**	**16.1**	**26**	**17.1**
Clostridium innocuum	2	1.6	8	5.3
Clostridium ramosum	2	1.6	1	0.7
Eubacterium	3	2.4	2	1.3
Eubacterium lentum	3	2.4	8	5.3
Lactobacillus plantarum	3	2.4	0	0.0
Propionibacterium acnes	0	0.0	2	1.3
gram-negative anaerobic cocci	**0**	**0.0**	**2**	**1.3**
gram-negative anaerobic bacilli	**7**	**5.6**	**2**	**1.3**
Porphyromonas asaccharolytica	3	2.4	0	0.0
gram-negative anaerobic bacillus	2	1.6	0	0.0
gram-negative anaerobic coccobacilli	**29**	**23.4**	**41**	**27.0**
Bacteroides distasonis	1	0.8	4	2.6
Bacteroides fragilis	9	7.3	12	7.9
Bacteroides ovatus	3	2.4	3	2.0
Bacteroides stercoris	1	0.8	2	1.3
Bacteroides thetaiotaomicron	5	4.0	10	6.6
Bacteroides uniformis	2	1.6	3	2.0
Bacteroides vulgatus	4	3.2	3	2.0
gram-negative bacilli	**1**	**0.8**	**2**	**1.3**
gram-negative bacillus	1	0.8	2	1.3

*Isolates obtained from surgical site infection or anastomotic leak failures.

The number of documented pa hogens by pa hogen is a count of documented pathogens across all pa ients/pathogens. This number may be greater than the number of patients due to the possibility of a patient having a documented pathogen for more than 1 pathogen/strain.

N=Number of evaluable patients in each treatment group.

n=Number of patients with a documented pathogen in each treatment group.

m=Number of documented pathogens.

%=Number of documented pathogens / all pa hogens

Medical Officer's comment*: *In general, identified pathogens were fairly similar across the treatment groups with the exception of the Clostridium innocuum and Eubacterium lentum found more often in the cefotetan group.

On page 106 of the CSR, the Applicant stated that a review of the most frequently isolated pathogens revealed no strong evidence of a relationship between type of surgical infection and pathogens isolated. Enterococcus and *Enterococcus faecalis* were seen in a slightly higher

number in superficial incisional and organ/space infections in the cefotetan group but were evenly distributed across infection type in the ertapenem group. *Staphylococcus aureus* was isolated most frequently in superficial incisional infections in both groups and *Escherichia coli* was seen most frequently in patients with an anastomotic leak in both groups. *Bacteroides fragilis* was evenly distributed across infection types and *Bacteroides thetaiotaomicron* was seen most frequently in superficial incisional infections in the cefotetan group and evenly distributed across infection type in the ertapenem group. *Clostridium innocuum* and *Eubacterium lentum* isolated in the cefotetan group were isolated from superficial incisional infections.

The following Table 21 provides a listing of all the documented pathogens from a surgical source displayed by type of surgical site infection or anastomotic leak in the evaluable population.

Table 21: Documented Pathogens – Surgical Source (Isolates obtained from a surgical site infection or anastomotic leak failures) Displayed by Type of Surgical Site Infection or Anastomotic Leak (Evaluable Population) (Applicant Table 7-5 found on pages 107-112 of CSR)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338) n=3		Cefotetan (N=334) n=7		Ertapenem (N=338) n=5		Cefotetan (N=334) n=11		Ertapenem (N=338) n=17		Cefotetan (N=334) n=28		Ertapenem (N=338) n=5		Cefotetan (N=334) n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
All Documented Pathogens	11		19		21		27		43		71		49		34	
gram-positive aerobic cocci	3	(27.3)	7	(36.8)	4	(19.0)	13	(48.1)	22	(51.2)	20	(28.2)	13	(26.5)	11	(32.4)
Abiotrophia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Enterococcus	0	(0.0)	3	(15.8)	1	(4.8)	4	(14.8)	4	(9.3)	3	(4.2)	3	(6.1)	1	(2.9)
Enterococcus avium	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus durans	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus faecalis	1	(9.1)	1	(5.3)	0	(0.0)	0	(0.0)	2	(4.7)	4	(5.6)	1	(2.0)	5	(14.7)
Enterococcus faecium	0	(0.0)	1	(5.3)	0	(0.0)	1	(3.7)	1	(2.3)	0	(0.0)	0	(0.0)	1	(2.9)
Enterococcus gallinarum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Enterococcus raffinosus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus sp.	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcus	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	2	(2.8)	2	(4.1)	1	(2.9)
Staphylococcus aureus	1	(9.1)	1	(5.3)	1	(4.8)	1	(3.7)	7	(16.3)	6	(8.5)	0	(0.0)	2	(5.9)
Staphylococcus aureus MRSA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.7)	1	(1.4)	0	(0.0)	1	(2.9)
Staphylococcus aureus MSSA	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	3	(7.0)	2	(2.8)	0	(0.0)	1	(2.9)
Staphylococcus aureus Non Spec	0	(0.0)	1	(5.3)	1	(4.8)	1	(3.7)	2	(4.7)	3	(4.2)	0	(0.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338) n=3		Cefotetan (N=334) n=7		Ertapenem (N=338) n=5		Cefotetan (N=334) n=11		Ertapenem (N=338) n=17		Cefotetan (N=334) n=28		Ertapenem (N=338) n=5		Cefotetan (N=334) n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Staphylococcus epidermidis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	1	(1.4)	0	(0.0)	0	(0.0)
Staphylococcus sciuri	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Streptococcus	0	(0.0)	0	(0.0)	1	(4.8)	3	(11.1)	2	(4.7)	0	(0.0)	1	(2.0)	0	(0.0)
Streptococcus agalactiae	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	2	(2.8)	1	(2.0)	0	(0.0)
Streptococcus milleri	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Streptococcus viridans	1	(9.1)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.4)	2	(4.1)	1	(2.9)
gram-positive aerobic bacilli	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Corynebacterium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative aerobic bacilli	2	(18.2)	5	(26.3)	3	(14.3)	5	(18.5)	8	(18.6)	5	(7.0)	4	(8.2)	8	(23.5)
Acinetobacter baumannii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Aeromonas hydrophila	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Enterobacter aerogenes	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Enterobacter cloacae	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Escherichia coli	1	(9.1)	2	(10.5)	1	(4.8)	0	(0.0)	2	(4.7)	0	(0.0)	3	(6.1)	5	(14.7)
Klebsiella pneumoniae	0	(0.0)	1	(5.3)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Morganella morganii	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Proteus mirabilis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(7.0)	1	(1.4)	0	(0.0)	0	(0.0)
Pseudomonas	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pseudomonas aeruginosa	0	(0.0)	0	(0.0)	1	(4.8)	2	(7.4)	2	(4.7)	4	(5.6)	0	(0.0)	1	(2.9)
gram-positive anaerobic cocci	0	(0.0)	1	(5.3)	1	(4.8)	0	(0.0)	3	(7.0)	2	(2.8)	1	(2.0)	1	(2.9)
Anaerococcus prevotii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Peptostreptococcus anaerobius	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(2.9)
Peptostreptococcus magnus	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	2	(4.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peptostreptococcus micros	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Ruminococcus hansenii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
gram-positive anaerobic bacilli	0	(0.0)	2	(10.5)	5	(23.8)	2	(7.4)	5	(11.6)	20	(28.2)	10	(20.4)	2	(5.9)
Bifidobacterium catenulatum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(2.0)	0	(0.0)
Clostridium clostridiiforme	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium difficile	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium hastiforme	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Clostridium innocuum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	7	(9.9)	1	(2.0)	1	(2.9)
Clostridium nexile	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium perfringens	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium ramosum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	1	(1.4)	0	(0.0)	0	(0.0)
Eubacterium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	1	(1.4)	2	(4.1)	1	(2.9)
Eubacterium biforme	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Eubacterium lentum	0	(0.0)	0	(0.0)	1	(4.8)	1	(3.7)	1	(2.3)	7	(9.9)	1	(2.0)	0	(0.0)
Eubacterium limosum	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eubacterium tortuosum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Lactobacillus plantarum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	0	(0.0)	1	(2.0)	0	(0.0)
Propionibacterium acnes	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
gram-positive anaerobic bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
gram-negative anaerobic cocci	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Acidaminococcus fermentans	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Veillonella	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
gram-negative anaerobic bacilli	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.8)	5	(10.2)	0	(0.0)
Desulfovibrio fairfieldensis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Porphyromonas asaccharolytica	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Porphyromonas cangingivalis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Prevotella intermedia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Sutterella wadsworthensis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative anaerobic bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
gram-negative anaerobic coccobacilli	4	(36.4)	4	(21.1)	7	(33.3)	4	(14.8)	5	(11.6)	21	(29.6)	13	(26.5)	11	(32.4)
Bacteroides caccae	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Bacteroides capillosus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Bacteroides distasonis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(5.6)	1	(2.0)	0	(0.0)
Bacteroides fragilis	1	(9.1)	3	(15.8)	3	(14.3)	2	(7.4)	3	(7.0)	4	(5.6)	2	(4.1)	3	(8.8)
Bacteroides merdae	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	1	(2.9)
Bacteroides ovatus	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.8)	2	(4.1)	1	(2.9)
Bacteroides sp.	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Bacteroides stercoris	1	(9.1)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Bacteroides thetaiotaomicron	1	(9.1)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	8	(11.3)	2	(4.1)	2	(5.9)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Bacteroides uniformis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	1	(1.4)	1	(2.0)	1	(2.9)
Bacteroides vulgatus	0	(0.0)	1	(5.3)	2	(9.5)	1	(3.7)	0	(0.0)	1	(1.4)	2	(4.1)	0	(0.0)
Fusobacterium mortiferum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Fusobacterium russii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Fusobacterium varium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative bacilli	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
gram-negative bacillus	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
bacterial organisms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Bacteria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)

† Isolates obtained from surgical site infection or anastomotic leak failures.
The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.
N = Number of evaluable patients in each treatment group.
n = Number of patients with a documented pathogen from each source category in each treatment group.
m = Number of documented pathogens.
% = Number of documented pathogens / all pathogens.

***Medical Officer's comment*: In case the preceding table is used for marketing purposes, the M.O. submits one correction. The M.O. changed cefotetan Patient 2481 from a nonevaluable failure to an evaluable failure. Therefore, the preceding table should be amended in the following manner. Under the Cefotetan heading, include one additional superficial incisional infection due to the Gram-negative anaerobic coccobacillus, *Bacteroides uniformis*.**

On page 113 of the CSR, the Applicant states that all species of *Bacteroides* identified were susceptible to ertapenem but showed varying levels of resistance to cefotetan. *Clostridium innocuum* and *Eubacterium lentum* were generally susceptible to ertapenem but generally resistant to cefotetan. As expected, isolates of Enterococcus species and methicillin-resistant Staphylococcus aureus (MRSA) from both treatment groups exhibited a high prevalence of resistance to both study drugs.

***Medical Officer's comment*: The M.O. notes that approximately 3 times as many anaerobes were isolated from superficial incisional infections in the cefotetan group as compared with the ertapenem group. The M.O. notes that it is typically unusual to find anaerobes as pathogens in superficial incisional infections. Factors potentially contributing to the presence of anaerobes included: (1) wounds were from elective colorectal surgery patients, (2) fecal soiling may have contaminated some of the wounds, (3) nearly 20% of the study population had diabetes as a co-morbid condition, and (4) investigators may have inappropriately labeled**

deeper infections as "superficial incisional." Clinical isolates of Bacteroides species, Clostridium innocuum and Eubacterium lentum tended to be more susceptible to ertapenem than to cefotetan. This may explain the discrepancy in anaerobic pathogens observed between treatment groups. The Microbiology reviewer, Dr. Avery Goodwin, evaluated the susceptibility/resistance profiles of the isolated anaerobic pathogens and confirmed this finding. Please see his review for additional details.

The Applicant performed the following additional exploratory analyses. The Agency confirmed the results of these analyses. Statistical support provided by Yunfan Deng, Ph.D., Biostatistics Reviewer.

Table 22 shows analyses of outcomes by gender, age, and race.

Table 22. Adjusted Clinical Outcomes at Follow-up Displayed by Gender, Age, and Race/Ethnicity (Evaluable)

	Ertapenem (A) (N=346)			Cefotetan (B) (N=339)			Observed Differences (A-B)	
	Observed¥ Response			Observed¥ Response				
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Gender								
Female	107/153	70	(62.0, 77.1)	101/161	62.7	(54.8, 70.2)	7.2	(-3.2, 17.6)
Male	137/193	71	(64.0, 77.2)	93/178	52.2	(44.6, 59.8)	18.7	(9.0, 28.5)
Age								
< 65 years	134/195	68.7	(61.7, 75.1)	116/194	59.8	(52.5, 66.8)	8.9	(-0.6, 18.4)
≥ 65 years	110/151	72.8	(65.0, 79.8)	78/145	53.8	(45.3, 62.1)	19.1	(8.3, 29.8)
< 75 years	197/284	69.4	(63.6, 74.7)	164/287	57.1	(51.2, 62.9)	12.2	(4.4, 20.1)
≥ 75 years	47/62	75.8	(63.2, 85.8)	30/52	57.7	(43.2, 71.3)	18.1	(0.97, 35.3)
Race								
Hispanic	17/26	65.4	(44.3, 82.8)	10/24	41.7	(22.1, 63.4)	23.7	(-3.2, 50.6)
Black	27/40	67.5	(50.9, 81.4)	27/46	58.7	(43.2, 73.0)	8.8	(-11.5, 29.1)
White	195/272	71.7	(65.9, 77.0)	148/257	57.6	(51.2, 63.7)	14.1	(6.0, 22.2)
Other	5/8	62.5	-	9/12	75	-	-12.5	-

¥ Computed from a statistical model pooling across surgical procedure.

N = Number of Evaluable pa ients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.

CI = Confidence interval. Modified from Applicant's Table 7-8 of CSR, p 125.

Table 23 shows analyses of outcomes by type of bowel preparation.

Table 23. Adjusted Clinical Outcomes at Follow-up Displayed by Type of Bowel Preparation (Evaluable)

	Ertapenem (A) (N=346)			Cefotetan (B) (N=339)			Observed Differences (A-B)	
	Observed[¥] Response			Observed[¥] Response				
Bowel Preparation	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Sodium Phosphate	131/183	71.6	(64.5, 78.0)	122/191	63.9	(56.6, 70.7)	7.7	(-1.7, 17.2)
Polyethylene Glycol	112/162	69.1	(61.4, 76.1)	71/147	48.3	(40.0, 56.7)	20.8	(10.1, 31.6)
Overall	243/345	70.4	(65.3, 75.2)	193/338	57.1	(51.6, 62.4)	13.3	(6.2, 20.5)

[¥] Computed from a statistical model pooling across surgical procedure.

N = Number of Evaluable patients in each treatment group.

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

CI = Confidence interval.

One ertapenem patient and one cefotetan patient were excluded from this analysis because they were missing bowel preparation type values.

Modified from Applicant's Table 7-9 of CSR, p 126.

Table 24 shows analyses of outcomes by renal function.

Table 24. Adjusted Clinical Outcomes at Follow-up Displayed by Renal Function (Evaluable)

	Ertapenem (A) (N=346)			Cefotetan (B) (N=339)			Observed Differences (A-B)	
	Observed[¥] Response			Observed[¥] Response				
Creatinine Clearance Subgroup	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
≤ 30 mL/min/1.73m^2	3/4	75	-	4/5	80	-	-5.0	-
> 30 mL/min/1.73m^2	236/329	71.7	(66.5, 76.5)	184/323	57	(51.4, 62.4)	14.8	(7.5, 22.0)
Overall	239/333	71.8	(66.6, 76.5)	189/329	57.4	(51.9, 62.9)	14.3	(7.1, 21.5)

[¥] Computed from a statistical model pooling across surgical procedure.

N = Number of Evaluable patients in each treatment group.

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

CI = Confidence interval.

13 ertapenem patients and 10 cefotetan patients were excluded from this analysis because they were missing creatinine clearance values.

Adapted from Applicant's Table 7-10 of CSR, p 127.

Medical Officer's comment: There were no significant differences between treatment groups in the clinical response rates by age, gender, or race. For patients requiring dosage adjustments because of renal impairment, clinical response rates at follow-up were 75% for 4 clinically evaluable ertapenem patients and 80% for 5 clinically evaluable cefotetan patients. It is difficult to make any conclusive statements regarding the observed differences in response rates among patients requiring renal dose adjustment given the small sample size.

Table 25 shows the proportion of patients with favorable clinical response rates at the 4-week posttreatment assessment displayed by time from infusion of study medication to start of surgery stratified on whether this duration of time was less than or equal to 60 minutes or greater than 60 minutes.

Table 25. Observed Clinical Outcomes at Follow-up Stratified by Time from Study Therapy Infusion to Start of Surgery (< or = 60 mins vs. > 60 mins.) (Evaluable)

	Ertapenem (A) (N=346)			Cefotetan (B) (N=339)			Observed¥ Differences (A-B)	
	Observed¥ Response			Observed¥ Response				
Time from Study Therapy Infusion to Start of Surgery	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Evaluable								
≤ 60 mins.	141/198	71.2	(64.4, 77.4)	123/220	55.9	(49.1, 62.6)	15.3	(6.1, 24.2)
> 60 mins.	103/148	69.6	(61.5, 76.9)	71/119	59.7	(50.3, 68.6)	9.9	(-1.6, 21.4)
Overall	244/346	70.5	(65.4, 75.3)	194/339	57.2	(51.8, 62.6)	13.3	(6.1, 20.4)

¥ For overall, computed from a statistical model pooling across time from study medication start to start of surgery.

N = Number of Evaluable patients in each treatment group.

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

CI = Confidence interval.

Modified from Applicant's Table 8 of February 17, 2006 Response to FDA Request of January 6, 2006.

Medical Officer's comment: ***The results of this exploratory analysis do not differ significantly from those of the primary analysis.***

The following Table 26 shows the proportion of patients with favorable clinical response rates at the 4-week posttreatment assessment displayed by time from infusion of study medication to the end of surgery stratified on whether this duration of time was less than or equal to 4 hours or greater than 4 hours.

Table 26. Observed Clinical Outcomes at Follow-up Stratified by Time from Study Therapy Infusion to End of Surgery (< or = 4 hrs. vs. > 4 hrs.) (Evaluable)

Time from Study Therapy Infusion to Start of Surgery	Ertapenem (A) (N=346) Observed¥ Response n/m	%	(95% CI)	Cefotetan (B) (N=339) Observed¥ Response n/m	%	(95% CI)	Observed¥ Differences (A-B) %	(95% CI)
Evaluable								
≤ 4 hrs.	195/273	71.4	(65.7, 76.7)	168/275	61.1	(55.1, 66.9)	10.3	(2.4, 18.1)
> 4 hrs.	49/73	67.1	(55.1, 77.1)	26/64	40.6	(28.5, 53.6)	26.5	(9.8, 41.8)
Overall	244/346	70.5	(65.4, 75.3)	194/339	57.2	(51.8, 62.6)	13.3	(6.1, 20.4)

¥ For overall, computed from a statistical model pooling across time from study medication start to end of surgery.

N = Number of Evaluable patients in each treatment group.

n/m = Number of Evaluable patients with a favorable clinical assessment / number of Evaluable patients with assessment.
CI = Confidence interval.

Modified from Applicant's Table 6 of February 17, 2006 Response to FDA Request of January 6, 2006.

Medical Officer's comment: The M.O. notes that for surgeries lasting longer than 4 hours, ertapenem patients had a prophylactic success rate of 67.1% (49/73) and cefotetan patients had a success rate of 40.6% (26/64). The difference in prophylactic success of 26.5% is more than twice the difference observed in surgeries that lasted ≤ 4 hours (10.3%). The Division confirmed the results of this analysis. This analysis appears to concur with Dr. Bonapace's Biopharmaceutics analysis of Study 039 using historical MIC data on ertapenem and cefotetan. Therefore, in patients undergoing prolonged (> 4 hours) elective colorectal surgeries, ertapenem may have a theoretical advantage over cefotetan in prophylaxis against surgical site infections. This analysis provides another potential explanation for the overall lower prophylactic success rate observed in the group treated with cefotetan as compared with those given ertapenem. The Applicant should consider performing a second adequate and well-controlled clinical trial to confirm this exploratory analysis.

The Applicant performed two exploratory multivariate analyses. Tables 27 and 28 display the results of these analyses.

Table 27. Multivariate Analysis of Risk Factors for Favorable Clinical Response Rates (Evaluable Population) (adapted from Applicant Table 7-24 on page 161 of CSR)

Risk Factor	Adjusted OR	95% CI	p-value
Treatment (Ertapenem vs Cefotetan)	2.26	(1.59, 3.22)	<0.001
Tobacco Use (Current vs Non)	0.60	(0.38, 0.94)	0.082
Tobacco Use (Ex-user vs Non)	0.86	(0.58, 1.29)	
Occurrence of perforation/spillage (No vs Yes)	4.00	(1.40, 11.39)	0.010
Baseline albumin	1.39	(1.17, 1.66)	<0.001
Obese (Yes vs No)	0.54	(0.37, 0.78)	0.001
Duration of surgery	0.75	(0.63, 0.89)	0.001

The adjusted odds ratios (OR), 95% CIs, and p-values were estimated from a multiple logistic regression model using backward elimination. Odds ratios for the continuous variables represent the increased odds of a favorable clinical response based on a 1 standard deviation increase in the risk factor.
All factors displayed in this table remained in the final model (i.e., had a p-value <0.1).

Table 28. Multivariate Analysis of Risk Factors for Postoperative Infection Rates (Evaluable Population) (adapted from Applicant Table 7-27 on page 164 of CSR)

Risk Factor	Adjusted OR	95% CI	p-value
Treatment (Ertapenem vs Cefotetan)	0.40	(0.27, 0.59)	<0.001
Type of bowel preparation (Sodium Phosphate vs Polyethylene Glycol)	0.67	(0.45, 0.99)	0.047
Tobacco Use (Current vs Non)	2.08	(1.28, 3.40)	0.013
Tobacco Use (Ex-user vs Non)	1.30	(0.84, 2.02)	
Occurrence of perforation/spillage (No vs Yes)	0.28	(0.10, 0.79)	0.016
Site Shaved/Clipped (Immediately vs No)	0.49	(0.30, 0.78)	0.007
Site Shaved/Clipped (Not immediately vs No)	1.34	(0.27, 6.70)	
Baseline albumin	0.85	(0.71, 1.02)	0.087
Obese (Yes vs No)	2.15	(1.43, 3.21)	<0.001
Time from dosing to surgery	0.84	(0.69, 1.01)	0.069
Duration of surgery	1.33	(1.10, 1.61)	0.003

The adjusted odds ratios (OR), 95% CIs, and p-values were estimated from a multiple logistic regression model using backward elimination. Odds ratios for the continuous variables represent the increased odds of a postoperative infection based on a 1 standard deviation increase in the risk factor.
All factors displayed in this table remained in the final model (i.e., had a p-value <0.1).

Medical Officer's comment: (b) (4)

Medical Officer's comment: ***Overall, the results of these exploratory analyses are consistent with the results of the primary analyses indicating that ertapenem is noninferior to cefotetan for the prophylaxis of surgical site infections in elective colorectal surgery patients. It is difficult to make any conclusive statements based on these exploratory analyses beyond recommending that the Applicant consider further exploration of any or all of these exploratory endpoints as primary endpoints in dedicated, adequate and well-controlled clinical trials.*** (b) (4)

6.1.5 Clinical Microbiology

Avery Goodwin, Ph.D., the Clinical Microbiology reviewer for this supplement, had no additional recommendations for changes to the Applicant's proposed labeling for the prophylaxis against surgical site infection in elective colorectal surgery patients.

6.1.6 Efficacy Conclusions

In Study 039, the Applicant has demonstrated that a single 1 gram dose of ertapenem is noninferior to a single 2 gram dose of cefotetan for prophylaxis against surgical site infection in patients undergoing elective colorectal surgery. The results of this study support the approval of ertapenem for prophylaxis of surgical site infection following elective colorectal surgery.

The following additional conclusions may be drawn from the data that the Applicant provided from Study 039.

- (b) (4)
- (b) (4)
- The overall prophylaxis success rate in the cefotetan group was lower than had been observed in prior clinical studies. Potential reasons for this observation include (1) the increased prevalence of obesity among patients enrolled in Study 039, (2) varied definitions for the primary endpoint in other studies published between 1988 and 1992, and (3) prevalence of anaerobic pathogens isolated in the study resistant to cefotetan.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety analysis set in Study 039 includes all patients who received a dose of study drug. In this trial, 476 patients received a dose of ertapenem, and 476 patients received a dose of cefotetan.

Adverse events were recorded from study drug administration through to 14 days post-treatment. Laboratory testing of hematologic status and renal and hepatic function was performed within 30 days prior to study therapy, 48 hours prior to surgery, at least once post-operatively at Day 3-4 (or earlier if the patient was to be discharged before Day 3-4) and as clinically indicated, and at the 4-week follow-up visit if clinically indicated. The Applicant reported adverse events using MedDRA terminology.

The dose of ertapenem in this study is the same as is found in the approved labeling for complicated intra-abdominal infections and complicated skin and skin structure infections, as well as for the other infectious disease indications for which ertapenem is currently indicated for treatment in adult patients with normal renal function. The most frequently reported drug-related AE in patients receiving ertapenem was wound infection. Additional frequently reported adverse events (AEs) in patients receiving ertapenem were nausea, pyrexia, ileus, vomiting, wound infection, and pruritus. The overall safety profile for ertapenem is similar to that of cefotetan.

The Applicant updated the **ADVERSE REACTIONS** section of the proposed labeling by including the following:

"In a clinical study in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of ertapenem 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall adverse experience profile was generally comparable to that observed for ertapenem in previous clinical trials. Table 7 shows the incidence of adverse experiences other than those previously described above for ertapenem, regardless of causality, reported in ≥ 1.0% of patients in this study.

Table 7
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-up in >1.0% of Adult Patients Treated With INVANZ for Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Adverse Events	INVANZ 1 g (N=476)	Cefotetan 2 g (N=476)
		(b) (4)

Additional adverse experiences that were reported in this prophylaxis study with INVANZ, regardless of causality, with an incidence <1.0% and >0.5% within each body system are listed below:

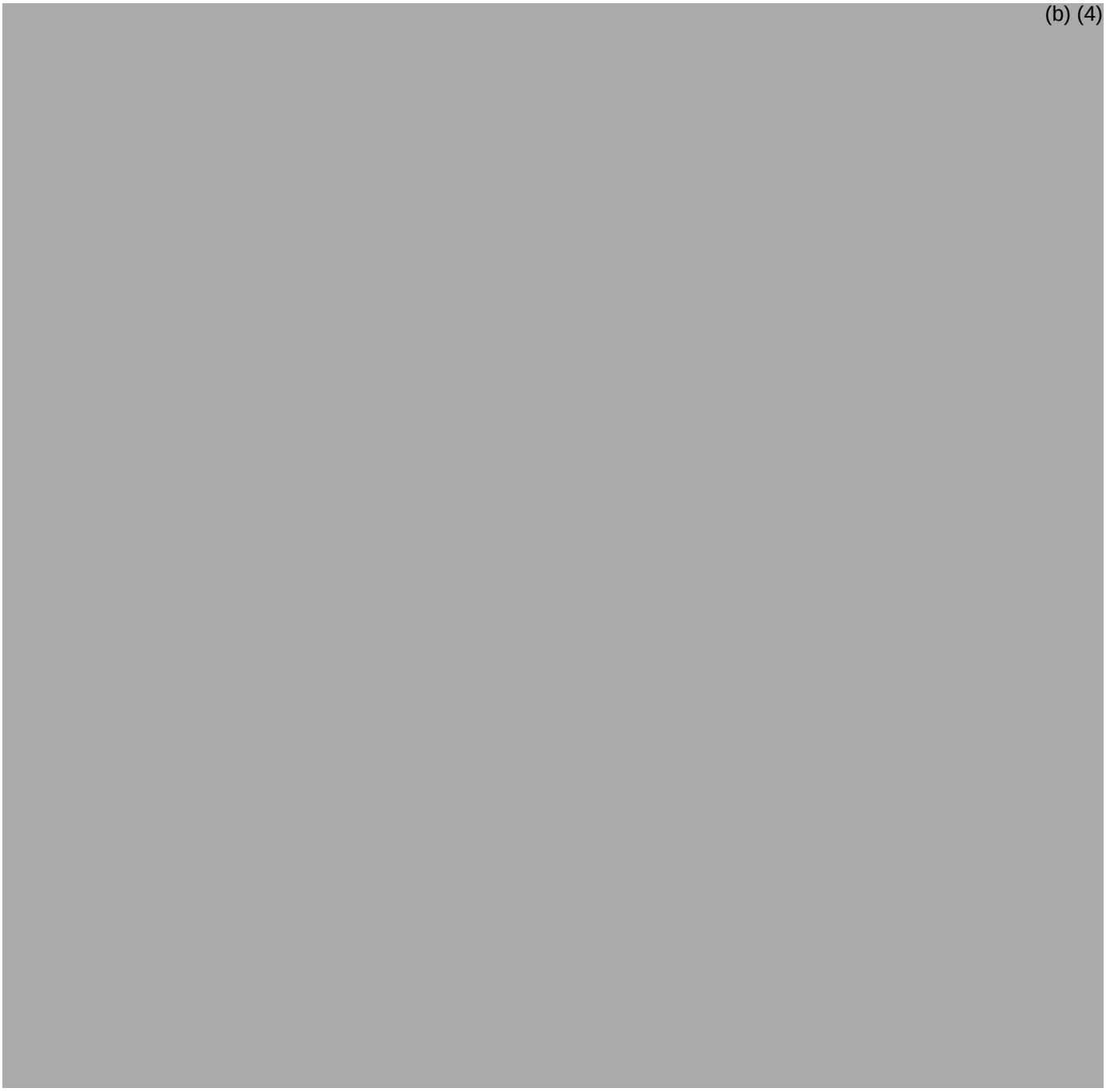
Gastrointestinal Disorders: dry mouth, hematochezia;
General Disorders and Administration Site Condition: crepitations;
Infections and Infestations: abdominal abscess, fungal rash, pelvic abscess;
Injury, Poisoning and Procedural Complications: incision site complication, incision site hemorrhage, intestinal stoma complication;
Musculoskeletal and Connective Tissue Disorders: muscle spasms;
Nervous System Disorders: cerebrovascular accident;
Renal and Urinary Disorders: pollakiuria;
Respiratory, Thoracic and Mediastinal Disorders: crackles lung, lung infiltration, pulmonary congestion, pulmonary embolism, wheezing."

Additionally, under *Adverse Laboratory Changes*, the Applicant included the following.

"In a clinical study in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of ertapenem 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall laboratory adverse experience profile was generally comparable to that observed for ertapenem in previous clinical trials. Additional laboratory adverse experiences that were reported during therapy and the 14 days post surgery period (b) (4) patients, regardless of causality, include: white blood cell count increased and urine protein present."

Medical Officer's comment: The M.O. recommends the following changes in the safety labeling for ertapenem based on review of the findings of this study.

(b) (4)



7.1.1 Deaths

The Applicant reported 10 deaths among the 952 patients who received study drug, including 3 of 476 (0.63%) ertapenem recipients and 7 of 476 (1.5%) cefotetan recipients. Two of the three deaths in the ertapenem group and five of the seven deaths in the cefotetan group were in patients 70 years of age or older. All of the deaths in both treatment groups occurred after the completion of study therapy (ertapenem: median = 7 days, range 4 to 13 days; cefotetan: median

= 8 days, range 2 to 14 days). Deaths in ertapenem recipients were attributed to: pulmonary embolism (1 patient), pulmonary edema (1 patient), and respiratory failure (1 patient). None of the deaths in either treatment group were considered by the investigators to be drug-related.

Medical Officer's comments: ***This Medical Officer (M.O.) reviewed the CRFs and summaries of these patients and concurs with the investigators' assessments.***

The M.O. notes that Patient 2122, aged 41 years, was diagnosed with and died from a pulmonary embolism 7 days post ertapenem therapy. The patient had multiple risk factors for pulmonary embolism, including a history of ongoing tobacco use, hypertension, obesity, and recent surgery. The M.O. searched AERS DataMart for additional cases of pulmonary embolism among patients exposed to ertapenem. No additional cases were found.

The M.O. noted that out of the treated patients, 3/476 (0.6%) in the ertapenem group and 4/476 (0.8%) in the cefotetan group had pulmonary embolism noted as a serious adverse event. Given that most pulmonary emboli arise from deep venous thromboses, the M.O. evaluated the adverse event dataset for patients with deep venous thromboses. Based on this review, the M.O. found that 2/476 (0.4%) in the ertapenem group and 4/476 (0.8%) in the cefotetan group had deep venous thrombosis reported as an adverse event. One cefotetan patient, Patient 2151, was diagnosed with bilateral deep venous thromboses on (b) (6) ***and with pulmonary emboli on the following day,*** (b) (6) ***The patient was placed on anti-coagulation therapy and survived.***

The M.O. believes that the occurrence of deep venous thromboses and pulmonary emboli in Study 039 was more likely associated with surgical intervention and post operative inactivity than with exposure to the study treatments.

The Applicant has voluntarily added "pulmonary embolism" as an adverse experience, "…regardless of causality, with an incidence <1.0% and >0.5%...," to the proposed product labeling.

7.1.2 Other Serious Adverse Events

Table 29 shows the Medical Officer's analysis of nonfatal serious AEs (SAEs) in one or more patients in either group.

Table 29. Medical Officer's Analysis of Nonfatal Serious Adverse Events Occurring in One or More Patients in Either Treatment Group During Study Therapy and Follow-up

	Ertapenem (N=476)		Cefotetan (N=476)	
Specific Organ Class/Preferred Term	n	%	n	%
Patients with any nonfatal SAE	97	20.4	123	25.8
Blood and Lymphatic System Disorders	**1**	**0.2**	**2**	**0.4**
Anemia	1	0.2	2	0.4
Cardiac Disorders	**7**	**1.5**	**9**	**1.9**
Acute MI	0	0.0	1	0.2
Arrhythmia	1	0.2	2	0.4
Atrial fibrillation	1	0.2	3	0.6
Bradycardia	1	0.2	1	0.2
Cardiac failure, congestive	1	0.2	2	0.4
Coronary artery disease	1	0.2	0	0.0
Sinus Bradycardia	1	0.2	0	0.0
Sinus Tachycardia	1	0.2	0	0.0
Eye Disorders	**0**	**0.0**	**1**	**0.2**
Visual Disturbance	0	0.0	1	0.2
Gastrointestinal Disorders	**45**	**9.5**	**50**	**10.5**
Abdominal Pain	5	1.1	7	1.5
Bowel sounds abnormal	0	0.0	1	0.2
Diarrhea	2	0.4	1	0.2
Enterocutaneous fistula	0	0.0	1	0.2
Gastrointestinal hemorrhage	2	0.4	1	0.2
Gastrointestinal perforation	0	0.0	1	0.2
Hematochezia	1	0.2	0	0.0
Ileus	19	4.0	10	2.1
Ileus, paralytic	0	0.0	1	0.2
Intestinal obstruction	0	0.0	1	0.2
Intra-abdominal hemorrhage	0	0.0	3	0.6
Lower gastrointestinal hemorrhage	1	0.2	0	0.0
Nausea	3	0.6	3	0.6
Pancreatitis	2	0.4	1	0.2
Peritonitis	0	0.0	3	0.6
Rectal Discharge	1	0.2	0	0.0
Retroperitoneal hemorrhage	0	0.0	1	0.2
Small intestinal obstruction	7	1.5	8	1.7
Small intestinal perforation	0	0.0	1	0.2
Upper gastrointestinal hemorrhage	0	0.0	2	0.4
Vomiting	2	0.4	4	0.8
General Disorders and Administration Site Conditions	**3**	**0.6**	**2**	**0.4**
Adhesion	1	0.2	0	0.0
Chest pain	0	0.0	1	0.2
Multi-organ failure	0	0.0	1	0.2
Pyrexia	2	0.4	0	0.0
Hepatobiliary Disorders	**1**	**0.2**	**1**	**0.2**
Biloma	0	0.0	1	0.2
Cholecystitis	1	0.2	0	0.0
Infections and Infestations	**42**	**8.8**	**58**	**12.2**
Abdominal abscess	4	0.8	6	1.3
Abdominal infection	0	0.0	1	0.2
Abscess	1	0.2	1	0.2
Bacterial sepsis	1	0.2	1	0.2
Bronchial infection	0	0.0	1	0.2

Table 29. Medical Officer's Analysis of Nonfatal Serious Adverse Events Occurring in One or More Patients in Either Treatment Group During Study Therapy and Follow-up (cont'd)

	Ertapenem (N=476)		Cefotetan (N=476)	
Specific Organ Class/Preferred Term	n	%	n	%
Infections and Infestations (cont'd)	**42**	**8.8**	**58**	**12.2**
Cellulitis	1	0.2	2	0.4
Clostridium colitis	3	0.6	0	0.0
Colon, gangrene	0	0.0	1	0.2
Colostomy infection	1	0.2	0	0.0
Gastroenteritis	1	0.2	0	0.0
Infection	1	0.2	0	0.0
Pelvic abscess	4	0.8	2	0.4
Pelvic sepsis	0	0.0	1	0.2
Peritoneal abscess	0	0.0	1	0.2
Pneumonia	2	0.4	7	1.5
Pneumonia, Streptococcal	0	0.0	1	0.2
Postoperative infection	4	0.8	3	0.6
Respiratory tract infection	0	0.0	1	0.2
Sepsis	3	0.6	3	0.6
Septic shock	0	0.0	1	0.2
Staphylococcal bacteremia	1	0.2	0	0.0
Urinary tract infection	5	1.1	5	1.1
Wound infection	10	2.1	20	4.2
Injury, Poisoning, and Procedural Complications	**18**	**3.8**	**13**	**2.7**
Anastomotic complication	1	0.2	0	0.0
Anastomotic leak	7	1.5	4	0.8
Ankle fracture	1	0.2	0	0.0
Bladder injury	0	0.0	1	0.2
Intestinal stoma complication	2	0.4	0	0.0
Lumbar vertebral fracture	0	0.0	1	0.2
Overdose¥	1	0.2	1	0.2
Post procedural hemorrhage	0	0.0	1	0.2
Postoperative ileus	1	0.2	0	0.0
Seroma	1	0.2	1	0.2
Wound dehiscence	3	0.6	2	0.4
Wound evisceration	0	0.0	1	0.2
Wound secretion	1	0.2	1	0.2
Investigations	**3**	**0.6**	**9**	**1.9**
Blood bilirubin increased	1	0.2	0	0.0
Blood glucose decreased	0	0.0	1	0.2
Blood glucose increased	0	0.0	1	0.2
ECG-ST segment depression	0	0.0	1	0.2
Hematocrit decreased*	0	0.0	1	0.2
Hemoglobin decreased*	0	0.0	2	0.4
Nasogastric output, high	1	0.2	0	0.0
White blood cell count increased	1	0.2	3	0.6
Metabolism and Nutrition Disorders	**5**	**1.1**	**4**	**0.8**
Dehydration	3	0.6	4	0.8
Failure to Thrive	1	0.2	0	0.0
Hypovolemia	1	0.2	0	0.0
Musculoskeletal and Connective Tissue Disorders	**1**	**0.2**	**1**	**0.2**
Fistula	1	0.2	0	0.0
Pain in extremity	0	0.0	1	0.2

Table 29. Medical Officer's Analysis of Nonfatal Serious Adverse Events Occurring in One or More Patients in Either Treatment Group During Study Therapy and Follow-up (cont'd)

	Ertapenem (N=476)		Cefotetan (N=476)	
Specific Organ Class/Preferred Term	n	%	n	%
Neoplasms, Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1**	**0.2**	**0**	**0.0**
Carcinoid syndrome	1	0.2	0	0.0
Nervous system disorders	**5**	**1.1**	**3**	**0.6**
Aphasia	0	0.0	1	0.2
Cerebral infarction	0	0.0	1	0.2
Cerebrovascular accident	3	0.6	0	0.0
Convulsion	0	0.0	1	0.2
Hepatic encephalopathy	1	0.2	0	0.0
Loss of consciousness	1	0.2	0	0.0
Psychiatric Disorders	**0**	**0.0**	**3**	**0.6**
Confusional state	0	0.0	1	0.2
Disorientation	0	0.0	1	0.2
Mental status changes	0	0.0	1	0.2
Renal and Urinary Disorders	**3**	**0.6**	**3**	**0.6**
Hydronephrosis	1	0.2	0	0.0
Nephrolithiasis	1	0.2	0	0.0
Renal failure, acute	0	0.0	3	0.6
Urinary retention	1	0.2	0	0.0
Reproductive System and Breast Disorders	**1**	**0.2**	**2**	**0.4**
Female genital-digestive tract fistula	0	0.0	1	0.2
Pelvic Pain	1	0.2	0	0.0
Vaginal hemorrhage	0	0.0	1	0.2
Respiratory, Thoracic and Mediastinal Disorders	**9**	**1.9**	**9**	**1.9**
Dyspnea	2	0.4	2	0.4
Hypoxia	0	0.0	1	0.2
Pleural effusion	2	0.4	0	0.0
Pulmonary embolism	2	0.4	4	0.8
Pulmonary edema	1	0.2	0	0.0
Respiratory depression	1	0.2	0	0.0
Respiratory distress	1	0.2	0	0.0
Respiratory failure	0	0.0	2	0.4
Vascular Disorders	**2**	**0.4**	**8**	**1.7**
Deep vein thrombosis	1	0.2	4	0.8
Hematoma	0	0.0	1	0.2
Hemorrhage	0	0.0	1	0.2
Hypertension	0	0.0	1	0.2
Hypotension	1	0.2	0	0.0
Peripheral ischemia	0	0.0	1	0.2

Although a patient may have had more than one adverse experience, the patient is only counted once within a sub-category. The same patient may appear in different categories.

*Patient 2991 was reported as having both hematocrit decreased and hemoglobin decreased.

¥Patients 2261 and 2747 overdosed on narcotics, not study drug.

<u>Medical Officer's comments</u>: The Medical Officer found 147 nonfatal SAEs among 97 patients in the ertapenem group (20.4% of treated patients) and 181 nonfatal SAEs among 123 patients in the cefotetan group (25.8% of treated patients). These findings are consistent with the Applicant's findings in Table 8-6, excluding fatal SAEs. Fatal SAEs were discussed in

Section 7.1.1. In addition, the Medical Officer's table includes SAEs due to laboratory abnormalities.

The nonfatal SAE profiles were generally similar between the two study groups.

The most common nonfatal SAEs were ileus and wound infection, both of which are common complications of colorectal surgery. Ileus occurred in 19 (4.0%) of ertapenem patients and 10 (2.1%) of cefotetan patients. Wound infection occurred in 10 (2.1%) of ertapenem patients and 20 (4.2%) of cefotetan patients.

Other notable nonfatal SAEs observed in the ertapenem group were: "Bradycardia" (Patient 2098, discussed in further detail in Section 7.1.6); "Sinus Bradycardia" (Patient 2710, discussed in further detail in Section 7.1.6); "Clostridium colitis" (Patients 2289, 2072, and 3676, discussed in further detail in Section 7.1.5); and "Blood bilirubin increased" and "Hepatic encephalopathy"(Patient 2167, discussed in Section 7.1.7.3).

The vast majority of nonfatal SAEs in the ertapenem group appeared to be due to patients' underlying co-morbid conditions, including malignant cancer, concomitant medications, and post-operative status. This includes Patient 2122's pulmonary embolism; the cerebrovascular accidents observed in Patients 2166, 2520, and 2725; the pancreatitis observed in Patients 2788 and 3694; and Patient 2255's hematochezia.

Patient 2301 from study site 40 experienced 7 nonfatal SAEs. These included abdominal pain and sinus tachycardia on post-operative day (POD) 1, nausea (POD 3), pelvic pain (POD 4), atrial fibrillation (POD 6), gastrointestinal hemorrhage (POD 9), and another episode of nausea (POD 12). Patient 2301 had a combined sigmoidectomy and rectectomy for a rectal malignant neoplasm. According to the Patient's CRF, the surgery on (b) (6) was uneventful, that is, the surgeon noted no inadvertent perforation of the colon or spillage of the luminal contents. However on (b) (6) the patient was noted to have a presacral fluid collection and was placed on levofloxacin. The patient had CT-guided aspiration of the fluid collection on (b) (6) and was deemed a clinical failure by the study investigator. Cultures of the aspirate were negative; however the levofloxacin was continued until (b) (6). The M.O. believes that the majority of the patient's non-fatal SAE's were most likely associated with failure of prophylaxis and not likely a consequence of the pre-operative dose of ertapenem.

The M.O. notes that no seizures, renal failures, exacerbations of renal failure, elevations in AST or ALT, or neutropenia were noted in the ertapenem group as nonfatal SAEs.

7.1.3 Dropouts and Other Significant Adverse Events

The Medical Officer searched the Applicant's Adverse Event dataset for patients who withdrew due to an adverse event. Only one patient withdrew from Study 039 due to an adverse event. On page 233 of the CSR, the Applicant notes that Patient 3753, a 39 year old white male in the cefotetan group, "began experiencing hypersensitivity symptoms (a flushed face, watery eyes, sneezing, coughing, wheezing, and a splotchy chest) after receiving 12 mL (0.48 gm) of study

drug." The cefotetan infusion was interrupted and the patient was withdrawn from the study. The AE was considered mild in intensity and was thought to "probably" be related to study drug. The AE lasted 30 minutes, and the patient had a complete recovery. No patients in the ertapenem group discontinued study therapy due to an adverse event.

Medical Officer's comment: The Medical Officer notes that since Study 039 was a single dose study, patients who discontinued from study therapy due to an adverse event had to have their study therapy discontinued during the infusion. Due to this reason, it is not surprising that only one patient was withdrawn from Study 039 due to an AE.

Other significant adverse events are noted in sections 7.1.5, 7.1.6, and 7.1.7.3.

7.1.4 Other Search Strategies

The Medical Officer reviewed the Study 039 safety database for safety signals consistent with the safety section of the current product label for ertapenem. Particular attention was paid to any adverse event terminology that could have been related to seizures, renal dysfunction, liver enzyme elevation, neutropenia, *Clostridium difficile* infection or colitis, as well as all deaths, all withdrawals due to drug-related adverse events, and patients with clinically significant outlying laboratory abnormalities.

7.1.5 Common Adverse Events

At least one AE was reported in 357 patients (75.0%) in the ertapenem group and in 381 patients (80.0%) in the cefotetan group. Table 30 lists the AEs that were reported in at least 1% of the patients in either treatment group.

Overall, 738 out of 952 patients (77.5%) experienced adverse events during study drug therapy and the 14-day follow-up period.

Medical Officer's comment: To appropriately capture the true incidence of infection due to Clostridium difficile, the M.O. combined the MedDRA terms Clostridium difficile infection and Clostridium colitis to create a new term: Clostridium difficile infection or colitis. This new term is used in a number of the adverse event tables.

Table 30. Number (%) of Patients with Adverse Events (Incidence ≥ 1%) in At Least One Treatment Group by System Organ Class During Study Therapy and Follow-up Period
(modified from Applicant Table 11-31 on pages 443-453 of CSR)

	Ertapenem (N=476)		Cefotetan (N=476)	
	n	%	n	%
Patients with one or more adverse experiences	357	75.0	381	80.0
Patients with no adverse experiences	119	25.0	95	20.0
Blood and Lymphatic System Disorders	**27**	**5.7**	**36**	**7.6**
Anemia	27	5.7	33	6.9
Cardiac Disorders	**45**	**9.5**	**66**	**13.9**
Arrhythmia	5	1.1	3	0.6
Atrial Fibrillation	6	1.3	7	1.5
Cardiac failure congestive	3	0.6	8	1.7
Sinus Tachycardia	2	0.4	6	1.3
Tachycardia	26	5.5	38	8.0
Gastrointestinal Disorders	**200**	**42.0**	**196**	**41.2**
Abdominal Distension	23	4.8	12	2.5
Abdominal Pain	19	4.0	17	3.6
Constipation	14	2.9	7	1.5
Diarrhea	27	5.7	15	3.2
Dyspepsia	16	3.4	17	3.6
Flatulence	8	1.7	2	0.4
Gastroesophageal Reflux Disease	2	0.4	5	1.1
Ileus	55	11.6	45	9.5
Nausea	95	20.0	121	25.4
Small Intestinal Obstruction	10	2.1	9	1.9
Vomiting	54	11.3	52	10.9
General Disorders and Administration Site Conditions	**119**	**25.0**	**114**	**23.9**
Asthenia	5	1.1	4	0.8
Chest pain	10	2.1	6	1.3
Hyperthermia	6	1.3	8	1.7
Edema	5	1.1	2	0.4
Edema, peripheral	12	2.5	14	2.9
Pyrexia	72	15.1	64	13.4
Infections and Infestations	**100**	**21.0**	**142**	**29.8**
Abdominal abscess	4	0.8	6	1.3
Cellulitis	7	1.5	7	1.5
Clostridium difficile infection or colitis*	8	1.7	3	0.6
Pneumonia	10	2.1	19	4.0
Postoperative infection	11	2.3	19	4.0
Sepsis	5	1.1	4	0.8
Urinary tract infection	18	3.8	26	5.5
Wound infection	31	6.5	59	12.4

*The M.O. combined the MedDRA terms *Clostridium difficile* infec ion and Clostridium colitis to create the new term: *Clostridium difficile* infection or colitis.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a System Organ Class (SOC) category. The same patient may appear in different categories.

Table 30. (continued) Number (%) of Patients with Adverse Events (Incidence ≥ 1%) in At Least One Treatment Group by System Organ Class During Study Therapy and Follow-up Period (modified from Applicant Table 11-31 on pages 443-453 of CSR)

	Ertapenem (N=476)		**Cefotetan** (N=476)	
	n	%	n	%
Injury, Poisoning and Procedural Complications	**63**	**13.2**	**63**	**13.2**
Anastomotic leak	7	1.5	6	1.3
Post procedural pain	5	1.1	7	1.5
Seroma	6	1.3	9	1.9
Wound complication	14	2.9	11	2.3
Wound dehiscence	6	1.3	7	1.5
Wound secretion	9	1.9	10	2.1
Investigations	**118**	**24.8**	**131**	**27.5**
Alanine aminotransferase increased	5	1.1	4	0.8
Aspartate aminotransferase increased	5	1.1	5	1.1
Blood albumin decreased	6	1.3	11	2.3
Blood bilirubin increased	6	1.3	4	0.8
Blood calcium decreased	5	1.1	10	2.1
Blood glucose increased	5	1.1	7	1.5
Blood magnesium decreased	15	3.2	20	4.2
Blood phosphorus decreased	8	1.7	12	2.5
Blood potassium decreased	34	7.1	43	9.0
Blood sodium decreased	8	1.7	5	1.1
Haematocrit decreased	5	1.1	13	2.7
Haemoglobin decreased	4	0.8	13	2.7
Heart rate increased	8	1.7	4	0.8
Oxygen saturation decreased	7	1.5	8	1.7
Protein urine present	5	1.1	2	0.4
Prothrombin time prolonged	4	0.8	5	1.1
Red blood cells urine positive	6	1.3	4	0.8
White blood cell count increased	22	4.6	24	5.0
Metabolism and Nutrition Disorders	**19**	**4.0**	**28**	**5.9**
Dehydration	4	0.8	7	1.5
Malnutrition	2	0.4	7	1.5
Musculoskeletal and Connective Tissue Disorders	**27**	**5.7**	**27**	**5.7**
Back pain	9	1.9	5	1.1
Muscle spasms	4	0.8	5	1.1
Pain in extremity	4	0.8	10	2.1
Nervous System Disorders	**55**	**11.6**	**61**	**12.8**
Dizziness	12	2.5	11	2.3
Headache	16	3.4	23	4.8
Hypoaesthesia	17	3.6	25	5.3

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a System Organ Class (SOC) category. The same patient may appear in different categories.

Table 30. (continued) Number (%) of Patients with Adverse Events (Incidence ≥ 1%) in At Least One Treatment Group by System Organ Class During Study Therapy and Follow-up Period (modified from Applicant Table 11-31 on pages 443-453 of CSR)

	Ertapenem (N=476)		**Cefotetan** (N=476)	
	n	%	n	%
Psychiatric Disorders	**42**	**8.8**	**55**	**11.6**
Anxiety	7	1.5	16	3.4
Confusional state	18	3.8	15	3.2
Insomnia	12	2.5	17	3.6
Renal and Urinary Disorders	**59**	**12.4**	**62**	**13.0**
Dysuria	5	1.1	6	1.3
Hematuria	4	0.8	8	1.7
Oliguria	25	5.3	26	5.5
Renal failure, acute	0	0.0	5	1.1
Urinary retention	17	3.6	8	1.7
Reproductive System and Breast Disorders	**6**	**1.3**	**10**	**2.1**
Respiratory, Thoracic and Mediastinal Disorders	**92**	**19.3**	**87**	**18.3**
Atelectasis	16	3.4	9	1.9
Cough	5	1.1	6	1.3
Dyspnea	15	3.2	21	4.4
Hiccups	6	1.3	5	1.1
Hypoxia	5	1.1	4	0.8
Pharyngolaryngeal pain	15	3.2	11	2.3
Pleural effusion	15	3.2	15	3.2
Pulmonary edema	2	0.4	5	1.1
Rales	8	1.7	4	0.8
Skin and Subcutaneous Tissue Disorders	**57**	**12.0**	**58**	**12.2**
Erythema	9	1.9	11	2.3
Hyperhidrosis	5	1.1	3	0.6
Pruritus	31	6.5	27	5.7
Rash	6	1.3	8	1.7
Vascular Disorders	**41**	**8.6**	**61**	**12.8**
Hypertension	20	4.2	27	5.7
Hypotension	16	3.4	19	4.0

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a System Organ Class (SOC) category. The same patient may appear in different categories.

Medical Officer's comments: ***The most commonly reported AEs in ertapenem patients were nausea, pyrexia, ileus, vomiting, wound infection, and pruritus. The most commonly reported AEs in cefotetan patients were nausea, pyrexia, wound infection, vomiting, ileus, and tachycardia. The incidences of specific AEs were generally similar between groups. Most AEs occurred during the post-treatment period (as this was a single dose study), and most were described as mild to moderate in intensity.***

Less common adverse events are discussed in section 7.1.6.

Patients diagnosed with *Clostridium difficile* infections and/or colitis:

Eight patients in the ertapenem group and three patients in the cefotetan group experienced *Clostridium difficile* infection and/or colitis.

For the ertapenem group, Patients: 2889 (Site 051), 2330 (Site 034), 3645 (Site 005), 3662 (Site 008) experienced "Clostridial infection," and Patients: 2072 (Site 036), 2289 (Site 014), 2635 (Site 014), and 3676 (Site 036) experienced "Clostridium colitis." Study investigators reported that the *Clostridium difficile* infections and/or colitis were study drug-related adverse events in the following five patients: Patients 2289 (definite), 2635 (definite), 3645 (probable), 2330 (possible), and 3676 (possible).

For the cefotetan group, Patients: 2097 (Site 014) and 3673 (Site 036) experienced "Clostridial infection" and Patient 2632 (Site 007) experienced "Clostridium colitis." The study investigator reported that the following patient had a study drug-related adverse event: Patient 2097 (probable).

Ertapenem patients who developed *Clostridium difficile* infection and/or colitis:
Patient 2289 was an 80 year old White female diagnosed with pseudomembranous colitis 5 days after an ileocolectomy for cecal cancer. Her bowel preparation was oral polyethylene glycol solution (PEG). She received ertapenem on (b) (6). The pseudomembranous colitis was diagnosed on (b) (6) and was treated with metronidazole from (b) (6). Patient 2289 received no other concomitant antibiotics prior to the diagnosis of pseudomembranous colitis. The investigator noted that the ertapenem "definitely" caused the adverse event.

Patient 2330 was an 84 year old White male diagnosed with *Clostridium difficile* infection 5 days after a hemicolectomy for a colonic malignant neoplasm. His bowel preparation was oral sodium phosphate solution (SPS). The patient received both ertapenem and cefotetan on (b) (6) The *Clostridium difficile* infection was diagnosed on (b) (6) and was treated with metronidazole from (b) (6). Patient 2330 received no other concomitant antibiotics prior to the diagnosis of *Clostridium difficile* infection. The investigator noted that the ertapenem "possibly" caused the adverse event.

Patient 2889 was a 62 year old White male diagnosed with *Clostridium difficile* infection 4 days after a rectectomy and sigmoidectomy for a rectal malignant neoplasm. His bowel preparation was PEG. The patient received ertapenem on (b) (6) The *Clostridium difficile* infection was

diagnosed on (b) (6) and was treated with metronidazole from (b) (6). Patient 2889 received no other concomitant antibiotics prior to the diagnosis of *Clostridium difficile* infection. The investigator noted that the ertapenem was "definitely not" the cause of the adverse event.

Patient 3645 was an 86 year old White male diagnosed with *Clostridium difficile* infection 11 days after a colectomy with appendectomy for a colonic malignant neoplasm. His bowel preparation was SPS. The patient received ertapenem on (b) (6) The *Clostridium difficile* infection was diagnosed on (b) (6) and was treated with metronidazole from (b) (6) Patient 3645 received the following additional concomitant antibacterial agents prior to the diagnosis of *Clostridium difficile* infection: ceftriaxone (b) (6) and levofloxacin ((b) (6)) for pneumonia. The investigator noted that the ertapenem "probably" caused the adverse event.

Patient 3662 was a 54 year old White male diagnosed with *Clostridium difficile* infection 4 days after a hemicolectomy for a colonic malignant neoplasm. His bowel preparation was SPS. The patient received ertapenem on (b) (6). The *Clostridium difficile* infection was diagnosed on (b) (6) and was treated with metronidazole from (b) (6) Patient 3662 received no other concomitant antibiotics prior to the diagnosis of *Clostridium difficile* infection. The investigator noted that the ertapenem was "definitely not" the cause of the adverse event.

Patient 2072 was a 78 year old White male diagnosed with *Clostridium difficile* colitis on (b) (6) four days after a hemicolectomy for a colonic malignant neoplasm. His bowel preparation was SPS. The patient received ertapenem on (b) (6) and was treated with metronidazole from (b) (6). Patient 2072 received no other concomitant antibacterial agents prior to the diagnosis of *Clostridium difficile* colitis. On (b) (6) the *Clostridium difficile* colitis was down-graded from a serious adverse event to a non-serious adverse event. The investigator noted that the ertapenem was "definitely not" and "probably not" the cause of the adverse event, respectively.

Patient 2635 was a 74 year old White male diagnosed with *Clostridium difficile* colitis 3 days after a sigmoidectomy for a colonic malignant neoplasm. His bowel preparation was PEG. The patient received ertapenem on (b) (6) and was treated with metronidazole from (b) (6). Patient 2635 received no other concomitant antibiotics prior to the diagnosis of *Clostridium difficile* colitis. The investigator noted that the ertapenem "definitely" cause the adverse event.

Patient 3676 was a 79 year old White female diagnosed with *Clostridium difficile* colitis 6 days after a sigmoidectomy for intestinal diverticulitis. Her bowel preparation was SPS. The patient received ertapenem on (b) (6) and was treated with metronidazole from (b) (6). The patient also received oral vancomycin from (b) (6) to treat the *Clostridium difficile* colitis. Patient 3676 received no other concomitant antibiotics prior to the diagnosis of *Clostridium difficile* colitis. The investigator noted that the ertapenem "possibly" caused the adverse event.

Cefotetan patients who developed *Clostridium difficile* infection and/or colitis:

Patient 2097 was an 83 year old White female diagnosed with *Clostridium difficile* infection 9 days after a hemicolectomy for a colonic malignant neoplasm. Her bowel preparation was PEG. The patient received cefotetan on (b) (6) and was treated with metronidazole from (b) (6) Patient 2097 received no other concomitant antibacterial agents prior to the diagnosis of *Clostridium difficile* infection. The investigator noted that the cefotetan "probably" caused the adverse event.

Patient 3673 was a 72 year old White female diagnosed with *Clostridium difficile* infection 8 days after a partial colectomy for a colonic malignant neoplasm. Her bowel preparation was SPS. The patient received cefotetan on (b) (6) and was treated with metronidazole from (b) (6) (b) (6) Patient 3673 received no other concomitant antibacterial agents prior to the diagnosis of *Clostridium difficile* infection. The investigator noted that the cefotetan was "definitely not" the cause of the adverse event.

Patient 2632 was a 39 year old White male diagnosed with *Clostridium difficile* colitis 6 days after a sigmoidectomy for intestinal diverticulitis. His bowel preparation was SPS. The patient received cefotetan on (b) (6) and was treated with metronidazole from (b) (6). Patient 2632 received no other concomitant antibacterial agents prior to the diagnosis of *Clostridium difficile* colitis. The investigator noted that the cefotetan was "probably not" the cause of the adverse event.

Medical Officer's comment: The M.O. notes that two study centers, Sites 014 (in Arizona) and 036 (in Michigan) contained 54.5% (6/11) of the patients who experienced either "Clostridial infection" or "Clostridium colitis": 2097 (Site 014-Cefotetan), 2289 (Site 014-Ertapenem), 2635 (Site 014-Ertapenem), 2072 (Site-036-Ertapenem), 3673 (Site-036-Cefotetan), and 3676 (Site 036-Ertapenem). For these patients, this would suggest that in addition to the study drug exposure, a site-specific component such as an ongoing epidemic at these two sites concurrent with the study may have contributed to Clostridium difficile infection and/or colitis.

The M.O. found that the following five patients were not exposed to any additional antibacterial agents prior to the diagnosis of Clostridium difficile infection and/or colitis: 2072 (Site-036-ertapenem), 2632 (Site 007-cefotetan), 2889 (Site 051-ertapenem), 3662 (Site 008-ertapenem), and 3673 (Site-036-cefotetan). However, site investigators did not attribute these adverse events to study drug. The M.O. notes on page 91 of the study protocol that investigators were to record all medications, including antibiotics, taken by patients in the 14 days prior to study drug administration. It is possible that some of these patients may have been exposed to antibiotics > 14 days prior to surgery. However, the M.O. believes that it is also possible that study drug therapy was directly related to Clostridium difficile infection and/or colitis as none of these patients were exposed to any additional antibacterial agents from the time of study drug administration to the time of diagnosis of Clostridium difficile infection and/or colitis. The M.O. notes that 4/5 of these patients received oral sodium phosphate solution (SPS) for bowel preparation. The M.O. searched PubMed for references to published literature that spoke to an association between Clostridium difficile infection or colitis and prior use of SPS for bowel preparation. No references were found.

(b) (4)

[redacted]

Table 31 lists the AEs that were considered by investigators to be drug-related and that occurred in at least one patient in either treatment group. Drug-related AEs were reported in 6.9% of ertapenem patients and 8.4% of cefotetan patients. Wound infection was the most commonly reported drug-related AE in both treatment groups.

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Table 31. Drug-Related Adverse Events Occurring in at Least One Patient in Either Treatment Group (modified from Applicant Table 8-4 on page 172 of CSR)

	Ertapenem (N=476)		Cefotetan (N=476)	
Specific Organ Class/Preferred Term	n	%	n	%
Patients with any drug-related AEs	33	6.9	40	8.4
Cardiac Disorders	**1**	**0.2**	**0**	**0.0**
Sinus Bradycardia	1	0.2	0	0.0
Eye Disorders	**0**	**0.0**	**1**	**0.2**
Visual Disturbance	0	0.0	1	0.2
Gastrointestinal Disorders	**5**	**1.1**	**3**	**0.6**
Diarrhea	4	0.8	1	0.2
Nausea	1	0.2	2	0.4
General Disorders and Administration Site Conditions	**3**	**0.6**	**3**	**0.6**
Face edema	0	0.0	1	0.2
Infusion site burning	0	0.0	1	0.2
Pyrexia	3	0.6	1	0.2
Immune System Disorders	**0**	**0.0**	**1**	**0.2**
Hypersensitivity	0	0.0	1	0.2
Infections and Infestations	**17**	**3.6**	**19**	**4.0**
Candidiasis	0	0.0	1	0.2
Cellulitis	3	0.6	0	0.0
Clostridial infection	2	0.4	1	0.2
Clostridium colitis	3	0.6	0	0.0
Oral candidiasis	0	0.0	2	0.4
Pelvic abscess	0	0.0	1	0.2
Postoperative infection	1	0.2	3	0.6
Vaginal candidiasis	0	0.0	1	0.2
Wound infection	8	1.7	10	2.1
Injury, Poisoning and Procedural Complications	**3**	**0.6**	**6**	**1.3**
Seroma	0	0.0	1	0.2
Wound complication	3	0.6	2	0.4
Wound dehiscence	0	0.0	1	0.2
Wound secretion	0	0.0	3	0.6
Investigations	**3**	**0.6**	**9**	**1.9**
Activated partial thromboplastin time prolonged	1	0.2	3	0.6
ALT increased	1	0.2	3	0.6
AST increased	1	0.2	2	0.4
Bilirubin conjugated increased	0	0.0	1	0.2
Blood albumin decreased	0	0.0	1	0.2
Blood bilirubin increased	0	0.0	1	0.2
Platelet count decreased	0	0.0	1	0.2
Prothrombin time prolonged	1	0.2	4	0.8
White blood cell count increased	1	0.2	0	0.0
Psychiatric disorders	**1**	**0.2**	**0**	**0.0**
Confusional state	1	0.2	0	0.0
Reproductive System and Breast Disorders	**0**	**0.0**	**1**	**0.2**
Genital pruritus, female	0	0.0	1	0.2
Skin and Subcutaneous Tissue Disorders	**6**	**1.3**	**4**	**0.8**
Pruritus	4	0.8	2	0.4
Pruritus, generalized	0	0.0	1	0.2
Rash	2	0.4	1	0.2
Rash, erythematous	1	0.2	0	0.0
Urticaria	1	0.2	1	0.2
Vascular Disorders	**0**	**0.0**	**1**	**0.2**
Thrombophlebitis	0	0	1	0.2

Although a patient may have had 2 or more clinical adverse experiences, the patient is only counted once within a category. The same patient may appear in different categories.

Medical Officer's comments: ***Rates of drug-related adverse events in the two treatment groups were fairly similar. "Wound infection" was the most common drug-related adverse event in both study groups. Because of the relatively low incidence of drug-related adverse events, likely due to the single-dose nature of the study, little inference may be drawn from the following subgroup analyses based on gender, race, and age.***

In the ertapenem group, female and male patients experienced drug-related AEs at similar rates, 5.9% (12/204) versus 7.7% (21/272), respectively. With regard to race, 11.1% (1/9) of Asian patients, 8.0% (30/377) of White patients, 4.1% (2/49) of Black patients, and 0% (0/41) of Hispanic patients experienced drug-related AEs in the ertapenem group. With regard to age, 6.5% (17/262) of ertapenem patients less than 65 years of age, and 7.5% (16/214) ≥ 65 years of age experienced drug-related AEs.

In the cefotetan group, more females than males experienced drug-related AEs, 11.7% (25/213) versus 5.7% (15/263), respectively. With regard to race, 16.7% (6/36) of Hispanic patients, 15.4% (2/13) of Asian patients, 8.6% (31/362) of White patients, and 1.6% (1/62) of Black patients experienced drug-related AEs in the cefotetan group. With regard to age, 8.2% (23/279) of cefotetan patients less than 65 years of age, and 8.6% (17/197) ≥ 65 years of age experienced drug-related AEs.

The Medical Officer notes that a comparable number of patients in each group (1 ertapenem patient and 3 cefotetan patients) had drug-related elevations in the following liver enzyme studies: ALT and AST. No patients had drug-related elevations in alkaline phosphatase.

No specific drug-related AEs had enough patients in both treatment groups to make any meaningful comparisons.

Medical Officer's comments: ***The Applicant predefined seizure as a clinical adverse experience of special interest. The Medical Officer did not find evidence of any seizures occurring in ertapenem patients during study therapy or follow-up period. One patient (3711 at Site 018) in the cefotetan group had a seizure on Day 3. The seizure was not considered related to study therapy and did not cause discontinuation from the study.***

No patients in either the ertapenem or cefotetan group were reported as having neutropenia as a clinical adverse event.

Two patients in the ertapenem group (Patient-site: 2174-005, 2897-037) and two patients in the cefotetan group (2221-005, 2097-014) were reported as having renal failure, not otherwise specified. No patients in the ertapenem group were reported as having acute or chronic renal failure as a clinical adverse event. Five patients (2074-005, 2700-007, 3608-008, 2295-009, 2622-051) with acute renal failure and one patient (3726-065) with chronic renal failure were reported in the cefotetan group. One patient in the ertapenem group (3659-065) had acute pre-renal failure and one patient in the cefotetan group (2340-046) had renal tubular necrosis. Additionally, two patients in the ertapenem group (3687-008, 3734-008) and four patients in the cefotetan group (3701-002, 2866-007, 3688-008, 2936-041) were noted as

having "urine output decreased." None of these adverse events were attributable to study drug. The study population had multiple co-morbidities that would potentially predispose patients to acute renal failure or acute exacerbation of chronic renal failure post surgery. It was therefore difficult for the M.O. to attribute any worsening renal function directly to the study drug in these colorectal surgery patients.

7.1.6 Less Common Adverse Events

The following adverse events were noted in less than 1% of patients (regardless of attribution to study drug). These adverse events are categorized by specific organ class.

Table 32. Less Common Adverse Events Occurring in < 1% Patients in Either Treatment Group (adapted from Applicant Table 11-31 on pages 443-453 of CSR)

	Ertapenem (N=476)		Cefotetan (N=476)	
Specific Organ Class	n	%	n	%
Patients with one or more adverse experiences	357	75.0	381	80.0
Patients with no adverse experiences	119	25.0	95	20.0
Ear and Labyrinth Disorders	1	0.2	2	0.4
Endocrine Disorders	1	0.2	0	0.0
Eye Disorders	4	0.8	3	0.6
Hepatobiliary Disorders	4	0.8	3	0.6
Immune System Disorders	2	0.4	3	0.6
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	3	0.6	1	0.2
Surgical and Medical Procedures	0	0.0	2	0.4

Although a patient may have had more than one adverse experience, the patient is only counted once within a sub-category. The same patient may appear in different categories.

<u>Medical Officer's comments</u>: In general, the numbers of less common adverse events were similar in both treatment groups when analyzed by specific organ classes.

The M.O. further evaluated the following rare AEs in the ertapenem group.

Patient 2710 at study site 065 was a 76 year old White male who developed sinus bradycardia (heart rate = 45 beats/minute) for 6 minutes. This was considered a serious adverse event (SAE). The Patient was noted to also be hypotensive to 80/40 mmHg. The investigator noted that the bradycardia started as the drug infusion was completed, and stated that this serious adverse event (SAE) was "possibly" related to the study drug. The patient was discontinued from Study 039 due to this SAE. The narrative found on page 186 of the CSR states that Patient 2710 also had a history of atrioventricular block. The Medical Officer did not find a medical history of atrioventricular block in Patient 2710's CRF.

The M.O. queried the Applicant and received a reply on 3/23/06. The site investigator verified the presence of a first degree atrioventricular block as a pre-existing condition and stated that

the bradycardia was "probably" related to a "vagal reaction." The Applicant provided the following response.

> "Patient 2710 is a 76 year old white male with a medical history positive for hypertension (treated with Atenolol and Fosinopril beginning in 2003 and continuing at the time of study drug administration) and atrioventricular block. The patient was scheduled for elective colorectal surgery on (b) (6) and he received a single dose of ertapenem 1g infused over 30 minutes. As the infusion was completed, the patient's blood pressure dropped to 80/40 mmHg and pulse dropped to 45 beats per minute (sinus bradycardia). The patient was given IV ephedrine to bring his heart rate back up and transferred to the ICU where he stayed for approximately 6 hours for further monitoring. According to the investigator, the event was considered to be resolved in 6 minutes; the patient's remaining ICU stay was uneventful.
> At the time the serious adverse experience was reported to the Sponsor, the study site submitted a copy of their IRB notification form. Indicated on this report under the causality is a statement that "since drug has just finished being given it must be considered possibly related however PI feels it was probably a vagal reaction and pt has history of heart block". This medical history was inadvertently omitted from the case report form. Attached is a copy for your reference of the site notification to the IRB [Sec. 5.3.5.1: P039].
> Also attached are copies of three ECG reports for your reference [Sec. 5.3.5.1: P039]. The first ECG was obtained on (b) (6) prior to the planned administration of study medication; 1st degree A-V block was noted at this time. The second ECG was obtained on (b) (6) after administration of study medication; 1st degree A-V block is again noted. A third ECG from (b) (6), four days after administration of study medication, demonstrated a tracing similar to the earlier ones. No additional information is available."

Patient 2098 at study site 014 was a 55 year old White female who developed bradycardia and hypotension that began at 8:05 am and lasted for 20 minutes. Both were considered serious adverse events (SAEs). The patient's ertapenem infusion began at 7:15 am. The patient's surgery was cancelled and she was withdrawn from the study due to the bradycardia. The investigator noted that the bradycardia was "probably not" related to the study drug.

The M.O. queried the Applicant and received a reply on 3/23/06. The Applicant verified that the site investigator did not think that the bradycardia was due to study therapy, but instead was likely due to anesthetic agents given to the patient. The Applicant provided the following response.

> "Patient 2098 received one prophylactic dose of ertapenem infused over 30 minutes starting at 7:15 am, prior to the planned elective surgical procedure. Vital signs at the time of infusion were as follows: body temperature of 97.6 ^{o}F, pulse rate of 60 beats per minute, respiratory rate of 14 per minutes and blood pressure of 128/55 mmHg. The patient subsequently had a smooth induction with diprivan 100 mg at 7:50am in the operating room and was intubated without problems. Her heart rate on induction was 62 beats per minute, BP was 127/52 mmHg. At 8:05am her pulse fell to 49 beats per minute with systolic blood pressure 79 mmHg. The patient was treated with Ephedrine 10mg without increase in blood pressure or pulse. Phenylephrine infusion was started (10 mg in 250 ml normal saline) with increase in systolic BP to 104 mmHg. After induction of other anesthesia medications, her heart rate dropped to a rate of 25 beats per minute. She received a total of 0.6 mg atropine in divided doses increasing her pulse rate to 70 beats per minute and systolic BP to 134 mmHg. The surgical procedure was aborted at 8:30am. She was admitted to telemetry for cardiac work-up and cardiology testing did not reveal any significant findings. The reporting investigator felt that bradycardia was related to the anesthesia and definitely not related to study therapy. Specifically, the investigator specifically referenced

> Versed 2 mg, Fentanyl 150 mg, and Diprivan 100 mg as potentially causing the bradycardia. Attached for your reference is a copy of the original serious adverse event worksheet submitted by the site at the time of the event [Sec. 5.3.5.1: P039]. This worksheet shows the documented suspect medications."

The M.O. concurs with the Applicant's conclusions that the two cases of bradycardia were unlikely to be related to ertapenem therapy.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The following laboratory tests were performed within 30 days prior to study therapy, 48 hours prior to surgery, at least once post-operatively at Day 3-4 (or earlier if patient was to be discharged before Day 3-4) and as clinically indicated, and at the 4-week follow-up visit if clinically indicated.

Table 33. Laboratory Safety Tests (adapted from Applicant Table 5-3 on page 51 of CSR)

Hematology	Blood Chemistry	Urinalysis
Hemoglobin	Alanine transaminase (ALT)	Protein
Hematocrit	Aspartate transaminase (AST)	Glucose
White blood cell (WBC) count, Total and differential	Alkaline phosphatase	pH
Platelet Count	Total bilirubin*	Red blood cell (RBC) count
PT	Albumin	WBCs
PTT	Creatinine	Urine Casts Unspecified
INR	Blood urea nitrogen (BUN)	

*Bilirubin was fractionated (direct/indirect) if total bilirubin was greater than the upper limit of normal.

In the ertapenem group, 97.9% (466/476) of those treated had at least one baseline laboratory study. In the cefotetan group, 98.3% (468/476) of those treated had at least one baseline laboratory study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study 039 was a multicenter, randomized, double-blind trial which compared a single dose of ertapenem 1 gram IV with a single dose of cefotetan 2 grams IV for the prophylaxis of surgical site infection following elective colorectal surgery. In Study 039, 476 patients received ertapenem, and 476 patients received cefotetan. No safety data was pooled from other studies.

7.1.7.3 Standard analyses and explorations of laboratory data

Given the extensive experience with ertapenem use in the general adult population, the safety analysis of the laboratory data from Study 039 will focus on the following. The M.O. analyzed the safety data for adverse events due to laboratory abnormalities. This information is displayed in the following sections along with commentary from the Medical Officer. Additionally, the M.O. displays and discusses predefined clinically significant laboratory abnormalities (CSLA). Analyses include identification of outlying data for key hematologic and chemistry data. No patients withdrew due to laboratory adverse events.

Table 34 shows the proportions of patients with specific laboratory adverse events.

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Table 34. Number (%) of Patients with Specific Laboratory AEs (Incidence > 0% in At Least One Treatment Group by Laboratory Test Category During Study Therapy and Follow-up Period (adapted from Applicant Table 8-12 on pages 237-238 of CSR)

	Ertapenem (N=476)		**Cefotetan** (N=476)	
	n/m	%	n/m	%
Patients with one or more adverse experiences	101/466	21.7	123/468	26.3
Patients with no adverse experiences	365/466	78.3	345/468	73.7
Blood Chemistry Test	**69/460**	**15.0**	**85/464**	**18.3**
ALT increased	5/416	1.2	4/421	1.0
Alkaline phosphatase increased	2/415	0.5	1/422	0.2
AST increased	5/417	1.2	5/424	1.2
Blood a bumin decreased	6/412	1.5	11/421	2.6
Blood bicarbonate decreased	1/1	100.0	0/*	
Blood bilirubin increased	6/413	1.5	4/418	1.0
Blood calcium decreased	5/6	83.3	10/10	100.0
Blood creatinine increased	1/457	0.2	1/460	0.2
Blood glucose decreased	0/6	0.0	3/10	30.0
Blood glucose increased	5/6	83.3	7/10	70.0
Blood magnesium decreased	15/15	100.0	20/20	100.0
Blood magnesium increased	0/15	0.0	2/20	10.0
Blood phosphorus decreased	8/11	72.7	12/12	100.0
Blood phosphorus increased	0/11	0.0	1/12	8.3
Blood potassium decreased	33/36	91.7	42/49	85.7
Blood potassium increased	2/36	5.6	4/49	8.2
Blood sodium decreased	8/11	72.7	4/6	66.7
Blood sodium increased	0/11	0.0	1/6	16.7
Blood urea nitrogen (BUN) increased	0/454	0.0	2/459	0.4
Blood uric acid increased	0/*		1/1	100.0
Blood zinc decreased	0/*		1/1	100.0
Calcium ionized decreased	1/*		0/*	
Creatine phosphokinase increased	0/1	0.0	1/1	100.0
Direct bilirubin increased	0/152	0.0	2/152	1.3
Protein total decreased	0/1	0.0	2/3	66.7
Hematology Laboratory Test	**32/464**	**6.9**	**45/467**	**9.6**
Hematocrit decreased	5/464	1.1	13/465	2.8
Hemoglobin decreased	4/464	0.9	13/466	2.8
Neutrophil count increased	0/417	0.0	3/417	0.7
Platelet count decreased	1/460	0.2	3/459	0.7
Platelet count increased	1/460	0.2	0/459	0.0
Red blood cell count decreased	2/3	66.7	2/4	50.0
White blood cell count decreased	1/464	0.2	1/464	0.2
White blood cell count increased	22/464	4.7	24/464	5.2

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.

Although a pa ient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

*Indicated there was a laboratory AE wi h no associated laboratory test recorded postbaseline.

Table 34. (continued) Number (%) of Patients with Specific Laboratory AEs (Incidence > 0% in At Least One Treatment Group by Laboratory Test Category During Study Therapy and Follow-up Period (adapted from Applicant Table 8-12 on pages 237-238 of CSR)

	Ertapenem (N=476)		**Cefotetan** (N=476)	
	n/m	%	n/m	%
Hemostatic Function Test	**4/397**	**1.0**	**6/400**	**1.5**
Activated partial thromboplastin time prolonged	2/391	0.5	3/399	0.8
International normalized ratio increased	0/374	0.0	1/374	0.3
Prothrombin time prolonged	4/386	1.0	5/385	1.3
Urinalysis Test	**12/383**	**3.1**	**9/390**	**2.3**
Blood urine present	1/3	33.3	0/*	
Glucose urine present	0/380	0.0	2/389	0.5
Protein urine present	5/383	1.3	2/390	0.5
Red blood cells urine positive	6/325	1.8	4/358	1.1
Urine ketone body present	1/4	25.0	1/1	100.0
Urine leukocyte esterase positive	1/3	33.3	0/1	0.0
White blood cells urine positive	3/323	0.9	0/354	0.0

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.

Although a pa ient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

*Indicated there was a laboratory AE wi h no associated laboratory test recorded postbaseline.

<u>Medical Officer's comments</u>: Overall, more patients in the cefotetan group had laboratory AEs than in the ertapenem group, 26.3% versus 21.7%, respectively. The most common laboratory adverse experiences in both treatment groups were decreases in blood potassium and blood magnesium and an increase in white blood cell count. Differences in laboratory AEs between the two study treatment groups were minimal. When differences were noted, the numbers of patients with the laboratory studies were too few to draw any conclusions.

There were 9 patients with serious laboratory adverse experiences, 2 in the ertapenem group and 7 in the cefotetan group. None of these serious adverse experiences were considered drug-related and no patients were withdrawn as a result of a laboratory adverse experience.

Among those patients with specific laboratory AEs with an incidence of <u>≥</u> 1%, the M.O. noted the following. Six out of 413 (1.5%) of ertapenem patients (Patients 2167, 2242, 2255, 2734, 2774, and 2958) and 4/418 (1.0%) of cefotetan patients (Patients 2097, 2115, 2367, and 2733) had blood bilirubin increased. None of the ertapenem patients' increased bilirubin levels appeared to be directly attributable to study therapy. The ertapenem patients with increased bilirubin levels had several reasons for elevated bilirubin post-operatively: (1) all had multiple co-morbidities, (2) 83% had malignant cancer, and (3) most were on multiple medications pre-operatively, perioperatively, and postoperatively that may have contributed to rising levels. One ertapenem patient's increased bilirubin was considered a serious adverse event. This patient, Patient 2167, is discussed in further detail in the following paragraph.

Patient 2167 at Site 009 was a 49 year old Hispanic female who was noted as having increased blood bilirubin 4 days after receiving ertapenem. The patient's past medical history was significant for cirrhosis due to alcoholism, jaundice, and episodes of altered mentation. On (b) (6), Patient 2167 had a baseline total bilirubin = 0.9 mg/dL, direct bilirubin = 0.3 mg/dL, AST = 31, ALT = 29, albumin= 2.9 g/dL, PT = 13.7 sec, and PTT = 31.5 sec. The patient received 1 gram of ertapenem for a hemicolectomy for colonic malignant neoplasm on (b) (6) During the operation, the surgeon noted "liver cirrhosis" as an additional surgical finding. The investigator noted that the patient was encephalopathic on (b) (6) and follow-up blood work on (b) (6) demonstrated total bilirubin = 5.3 mg/dL, direct bilirubin = 3.2 mg/dL, AST = 52, ALT = 42, albumin= 2.4 g/dL, PT = 13.6 sec, and PTT = 33.8 sec. The bilirubin levels drifted downward thereafter. On (b) (6), total bilirubin = 1.3 mg/dL and direct bilirubin = 0.6. The site investigator stated that the elevated total bilirubin was "probably not" caused by the ertapenem dose. The M.O. notes that Patient 2167 received several potentially hepatotoxic agents prior to surgery, perioperatively, and postoperatively that could have exacerbated her hepatic dysfunction. These included, but were not limited to anesthetic agents and benzodiazepines. Therefore, the M.O. believes the patient's elevated bilirubin levels were due to a multifactorial insult, in which no one agent can be directly implicated.

The M.O. noted that 22/464 (4.7%) of ertapenem patients and 24/464 (5.2%) of cefotetan patients had "white blood cell count increased" noted as an adverse event during the course of the study. The M.O. found that the majority of these ertapenem patients with this adverse event were judged to be clinical failures by the study investigators. One of the ertapenem patient's increased white blood cell count was noted as a serious adverse event by the investigator. Patient 2473 at Site 040 was an 81 year old Hispanic male who was noted to have "leukocytosis" on (b) (6). On (b) (6) Patient 2473 had a baseline WBC = 9.2. The patient received 1 gram of ertapenem just prior to a sigmoidectomy for metastatic colon cancer. The surgeon noted ascities intraoperatively. On (b) (6) the patient had a WBC = 15.5 with 88% neutrophils. The patient received levofloxacin and metronidazole, was deemed a clinical failure, and no additional hematology was recorded in the CRF. The M.O. believes that the leukocytosis may have been due to bacterial peritonitis or other infectious etiology. The M.O. agrees with the investigator in that is highly unlikely that the leukocytosis was due to study drug.

The M.O. noted that 5/383 (1.3%) of ertapenem patients and 2/390 (0.5%) of cefotetan patients had "protein urine present" recorded as an adverse event during the course of the study. None of these adverse events were considered serious or study drug-related by the investigators. The M.O. notes that all of the ertapenem patients with "protein urine present" had multiple co-morbid conditions that may have predisposed patients to proteinuria and renal dysfunction, including diabetes mellitus and hypertension, and concurs that it was unlikely that these adverse events were directly the result of study drug use.

(b) (4)

Among those patients with specific laboratory AEs with an incidence of < 1%, the M.O. noted the following. Three ertapenem patients (Patient No.-Study Site: 2377-014, 2734-042, 2989-058) and no cefotetan patients had "white blood cells urine present." Patient 2377 at site 014 was an 81 year old White male who had a past medical history of "hematuria." The patient was on concomitant terazosin (reason not provided). On (b) (6) ***baseline urinalysis was negative for white blood cells (WBCs). The patient underwent a hemicolectomy for cecal cancer on*** (b) (6) ***On*** (b) (6) ***repeat urinalysis demonstrated "pyuria" and "proteinuria." The investigator stated that the pyuria was "probably not" related to study drug.***

Patient 2734 at site 042 was a 34 year old Hispanic male with a past medical history of "kidney infection." On (b) (6) ***baseline urinalysis demonstrated 2 red blood cells (RBCs) and 2 WBCs. The patient underwent a colectomy for diverticulitis on*** (b) (6) ***On*** (b) (6) ***repeat urinalysis demonstrated 25 WBCs, trace leukoesterase, and "large blood." No action was taken, and on*** (b) (6) ***repeat urinalysis demonstrated 10 RBCs and no WBCs. The investigator stated that the "increased white blood cells-urine" was "probably not" related to study drug.***

Patient 2989 at site 058 was a 27 year old Hispanic male with a past medical history of "congenital single kidney," as well as renal lithotripsy in the year before surgery. Baseline urinalysis on (b) (6) ***was "permanently missing." The patient underwent colectomy for ulcerative colitis on*** (b) (6) ***Repeat urinalysis on*** (b) (6) ***demonstrated 10 RBCs, 50 WBCs, and no protein. The patient was found to have a pelvic abscess on*** (b) (6) ***and was deemed a study failure. The investigator stated that the "increase urine WBC" was "definitely not" related to study drug.***

Though the M.O. cannot completely rule out that the "white blood cells urine present"(pyuria) in these three patients was not due to ertapenem, all three patients had medical histories of co-morbid conditions that may have been associated with pyuria. In addition, the M.O. suspects that these patients had foley catheters placed during their elective colorectal surgeries. Traumatic placement and or removal may have been associated with postoperative hematuria and pyuria.

With regard to key laboratory AEs related to renal and hepatic dysfunction, increases in blood creatinine, ALT, and AST did not differ significantly (p > 0.05) between the two treatment groups. Additional analyses will be displayed in the following sections.

The M.O. notes that increased total serum bilirubin is reported with an incidence of ≥ 1.0% in the "Adverse Laboratory Changes" section of the current ertapenem label.

7.1.7.4 Additional analyses and explorations

Patients in Study 039 had a number of co-morbid conditions, including but not limited to metastatic colon cancer. They only received a single dose of study therapy. Coupled with the fact that the majority of patients only had baseline labs and one set of postoperative labs performed during the course of the study, it was difficult to make any meaningful comparisons with regard to explorations for associations between laboratory adverse events and dose, time, drug-demographic, drug-disease, or drug-drug interactions beyond those already specified in this review**.**

7.1.7.5 Special assessments

The Applicant and Agency agreed upon a list of clinically significant laboratory abnormalities for hepatic, renal and hematologic function that would trigger further investigation and analysis.

The following table modified from the Applicant provides the number and percent of patients with a clinically significant laboratory abnormality by treatment group during hospitalization in the treated population. This table is modified from the Applicant's Table 8-17 found on page 250 of the CSR.

Table 35. Number (%) of Patients With a Clinically Significant Laboratory Abnormality During Hospitalization By Treatment Group (Treated Population) (adapted from Applicant's Table 8-17 found on page 250 of the CSR)

Laboratory Test	CSLA Criteria	Ertapenem N=476 n/m	%	Cefotetan N=476 n/m	%
Total serum bilirubin, mg/dL	>1.5 x ULN	20/403	5.0	18/407	4.4
	>2.5 x ULN	10/403	2.5	6/407	1.5
Serum direct bilirubin, mg/dL	>1.5 x ULN	14/129	10.9	12/130	9.2
	>2.5 x ULN	9/129	7.0	2/130	1.5
Serum alanine aminotransferase, IU	>2.5 x ULN	2/404	0.5	2/411	0.5
	>5.0 x ULN	0/404	0.0	2/411	0.5
Serum aspartate aminotrasferase, IU	>2.5 x ULN	3/406	0.7	4/414	1.0
	>5.0 x ULN	1/406	0.2	2/414	0.5
Serum a kaline phosphatase, IU	>2.5 x ULN	1/404	0.2	1/412	0.2
	>5.0 x ULN	0/404	0.0	0/412	0.0
Serum creatinine, mg/dL	>1.5 x ULN	4/449	0.8	7/454	1.5
	>3.0 x ULN	0/449	0.0	1/454	0.2
Absolute neutrophil count, ANC/microL	<1800	2/396	0.5	0/393	0.0
	<1000	0/396	0.0	0/393	0.0
	≤500	0/396	0.0	0/393	0.0
Platelet count 10^3/microL	<75	0/451	0.0	0/458	0.0
	<50	0/451	0.0	0/458	0.0
Hematocrit, %	<24	10/459	2.2	18/464	3.9
Hemoglobin, mg/dL	<8	12/458	2.6	17/464	3.7

N=Total number of patients in the treatment group.

n/m=Number of patients with CSLA/Number of patients with a baseline and at least one post baseline.

The same patient may appear in different categories.

***Medical Officer's comments:** Overall, the proportions of patients with clinically significant laboratory abnormalities (CLSAs) were similar between the two treatment groups. The most common CLSAs were elevated direct and total serum bilirubin.*

The M.O. notes that 11.1% of patients in the treated population had pre-existing hepatobiliary dysfunction. Fifteen patients in the ertapenem group had elevations in total bilirubin, direct bilirubin, or both to > 2.5 times the upper limit of normal (ULN). Ten ertapenem patients (Patient-study site: 2167-009, 2255-022, 2356-032, 2359-027, 2428-002, 2484-041, 2494-024, 2774-065, 2840-061, and 2958-022) had total serum bilirubin to > 2.5 x ULN. Nine patients in the ertapenem group (Patient-study site: 2167-009, 2359-027, 2764-054, 2774-065, 2849-064, 2913-065, 2958-022, 2985-009, and 3680-005) had elevations in direct bilirubin > 2.5 x ULN.

Four ertapenem patients (Patient-study site: 2167-009, 2359-027, 2774-065, and 2958-022) experienced elevations in both total and direct bilirubin to > 2.5 x ULN. None of these elevations were considered drug-related. All but three patients (Patient-study site: 2494-024, 2764-054, and 2774-065) had a prior medical history of liver disease or elevations in bilirubin levels at baseline. Patient 2494-024 was a 78 year old White male with a prior history of prostate cancer, cardiac arrhythmia, HTN, penicillin and sulfa allergies who had a hemicolectomy for a colonic malignant neoplasm. Baseline labs on (b) (6) were as follows: AST/ALT/Total bilirubin (TBILI)/alkaline phosphatase (ALK PHOS) = 26/26/0.4/126 (high). Concomitant medications included but were not limited to Tylenol (total daily dose unknown), propofol, fentanyl, morphine, and metoprolol. Repeat labs on (b) (6) were as follows: AST/ALT/TBILI/ALK PHOS = 41/39/3.5 (high)/164 (high). The patient was deemed a clinical failure ((b) (6)) due to a polymicrobial "organ/space infection" and "sepsis" with fecal drainage from the wound. He required three additional exploratory laparotomies that included fascial debridement and resection of a portion of the small bowel. No additional labs were recorded in the CRF. Patient 2764-054 was a 59 year old White male with a prior history of DM, HTN, hypercholesterolemia, coronary artery disease, and colon cancer who had a hemicolectomy and rectectomy for a rectal malignant neoplasm. Baseline labs on (b) (6) were as follows: AST/ALT/TBILI/ALK PHOS = 40/33/0.4/60. Concomitant medications included but were not limited to simvastatin, fenofibrate, glyburide, and pheneragan. Repeat labs on (b) (6) were as follows: AST/ALT/TBILI/ALK PHOS = 16/24/2.2 (high)/49. The patient was deemed a clinical failure on (b) (6) due to a "superficial incisional infection." No additional labs were recorded in the CRF. Patient 2774-065 was a 57 year old White male with a prior history of coronary artery disease, cerebrovascular accident, HTN, DM, chronic diarrhea, and "cancer" who had a rectectomy and sigmoidectomy for a rectal malignant neoplasm. Baseline labs on (b) (6) were as follows: AST/ALT/TBILI/ALK PHOS = -/-/0.4/- (no baseline AST/ALT/ALK PHOS). Concomitant medications included but were not limited to metformin, gemfibrozil, prozac, hydrocodone, and morphine. Repeat labs on (b) (6) were as follows: AST/ALT/TBILI/ALK PHOS = 96 (high)/79 (high)/3.4 (high)/-. Another set of repeat labs drawn on 4/27/04 revealed: AST/ALT/TBILI/ALK PHOS = 75 (high)/89 (high)/2.9 (high)/100. The patient was deemed a clinical failure on (b) (6) due to a urinary tract infection. The patient was also noted to have a presacral fluid collection/abscess that required drainage on (b) (6) No additional labs were recorded in the CRF.

While the M.O. cannot rule out that ertapenem may have played a role in the elevations of bilirubin, the M.O. noted that all three of these patients had malignant cancer of the colon and/or rectum, all three were exposed to potentially hepatotoxic medications during the perioperative period, and all three were deemed to be clinical failures due to infection.

The incidence of elevations in ALT and AST were infrequent and similar between the two treatment groups. In the ertapenem group, one patient developed an elevation in AST to > 5.0 x ULN. Patient 2806 at site 037, was a 68 year old white female with a history of a hepatic cyst and hepatic mass who at baseline had an AST=44 (1.3 x ULN) and an ALT=50 (within normal limits). Post-surgery (Study Day 5), she had an AST=242 (6.9 x ULN) and an ALT=165 (3.3 x ULN). The investigator did not consider these elevations to be adverse events. The M.O. cannot rule out that ertapenem may have played a role in the elevations of AST.

Other possible reasons for the elevations were exacerbation of the prior hepatic pathology during the surgery, and exposure to other potentially hepatotoxic medications during the perioperative period.

No ertapenem patients had elevations in ALT to > 5.0 x ULN.

Four patients in the ertapenem group (Patient-study site: 2167-009, 2342-033, 2261-034, and 2810-062) had elevations in serum creatinine to > 1.5 x ULN. None of these elevations were considered drug-related. The M.O. cannot rule out that ertapenem may have played a role in the creatinine elevations. Other possible reasons for the elevations included multiple co-morbid conditions, including but not limited to diabetes mellitus, coronary artery disease, and malignant cancer, and exposure to potentially nephrotoxic medications during the perioperative period. No patients in the ertapenem group had elevations to > 3.0 x ULN.

Two ertapenem patients (Patient-study site: 3702-002 and 2923-058) developed absolute neutrophil counts (ANC) < 1800/microL. Neither patient's decline in neutrophil count was considered an adverse event by the study investigators. Patient 3702 was a 56 year old white male who on (b) (6) ***had a baseline white blood cell count (WBC) = 6,200 with 61.7% neutrophils [calculated absolute neutrophil count (ANC)= 3,825]. On 12/17/04, the patient underwent a colectomy for colonic malignant neoplasm and splenectomy for splenic capsule tear. On*** (b) (6) ***repeat WBC = 4,500 with 32% neutrophils (calculated absolute neutrophil count = 1,440). The patient was deemed a clinical failure due to anastomotic leak with wound dehiscence, pneumonia, and urinary tract infection.***

Patient 2923 was a 30 year old Hispanic female who on (b) (6) ***had a baseline WBC = 6,600 with 65.9% neutrophils (calculated ANC = 4,349). On*** (b) (6) ***the patient underwent a rectectomy for ulcerative colitis. On*** (b) (6) ***repeat WBC = 2,400 with ANC = 1, 630 with 40% band neutrophils. The patient was deemed a clinical failure with an abdominal abscess and a central line infection.***

The M.O. cannot rule out that ertapenem may have played a role in these two cases of ANC's declining below 1,800/microL, however, another possible reason for the decline in ANC in both patients was overwhelming sepsis. The Applicant noted 4 additional patients with neutropenia to less than 500/microL. These included two ertapenem patients (Patient-study site: 2926-042 and 2060-034) and two cefotetan patients (Patient-study site: 2749-057 and 2821-057). On further review, the M.O. did not find any evidence for ANC's < 500/microL. In these patients, it appears that counts of band (immature) neutrophils were mistakenly counted as absolute neutrophil counts.

Ten of 459 (2.2%) ertapenem patients and 18/464 (3.9%) cefotetan patients had a decrease in hematocrit to < 24%. Twelve of 458 (2.6%) ertapenem patients and 17/464 (3.7%) cefotetan patients had a decrease in hemoglobin to < 8 mg/dL. Decreased hematocrit was reported as an adverse event in 5 ertapenem patients (Patient-study site: 2754-008, 2568-009, 2309-030, 2469-051, and 2542-051). Decreased hemoglobin was reported as an adverse event in 4 ertapenem patients (Patient-study site: 2003-005, 2568-009, 2469-051, and 2542-051). None of these

events were considered drug-related by investigators. The M.O. concurred that the cases of decreased hematocrit and hemoglobin were unlikely to be directly related to ertapenem use. These ertapenem patients had additional reasons for blood loss that included hematuria (Patient-study site: 2754-008, 2568-009, 2469-051, 2542-051, 2003-005), abdominal hematoma (2754-008), hematochezia (2309-030), and vaginal bleeding (2542-051).

The M.O. notes that increases in creatinine, AST, ALT, serum total bilirubin, and decreases in absolute neutrophil count, hematocrit and hemoglobin are included as Adverse Laboratory Changes in the current ertapenem label with incidences of ≥ 1.0%. Increases in direct serum bilirubin are included with an incidence of > 0.1% but < 1.0%. This is appropriate given the overall experience of patients treated with ertapenem across all Phase 2 and 3 studies.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign testing was performed at study entry, on the day of surgery, daily during hospitalization, on the day of hospital discharge, and at the 4-week follow-up visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign data from Study 039 were analyzed. The two treatment groups consisted of patients that received ertapenem and those that received cefotetan in a 1:1 randomization scheme.

7.1.8.3 Standard analyses and explorations of vital signs data

The following Table 36 provides the FDA's analysis of vital sign testing in Study 039 stratified by study period: baseline, at the time of study drug infusion, during post-operative hospitalization, and at the 4-week follow-up assessment. Central tendency is displayed using mean values and variance is displayed using standard deviation. Statistical support provided by Yunfan Deng, Ph.D., Biostatistics Reviewer.

Table 36. FDA Analysis of Vital Signs			
		Number of Patients*	
		Ertapenem	Cefotetan
Total Patients	BSL (N=860)	431	429
	IV TRT (N=805)	407	398
	Post TRT (N=936)	465	471
	Follow up (N=664)	345	319
Vital Signs		**Vital Sign Measurements**	
Pulse			
(beats/min)	BSL, Mean	75.6	77.6
	BSL, SD	12.1	13.1
	IV TRT, Mean	78.2	79.6
	IV TRT, SD	14.8	15.3
	Post TRT, Mean	83.8	85.5
	Post TRT, SD	11.5	11.7
	FU, Mean	78.2	80.7
	FU, SD	13.1	13.2
BP, Diastolic	BSL, Mean	75.6	75.4
(mm Hg)	BSL, SD	10.4	11.2
	IV TRT, Mean	73.1	72.0
	IV TRT, SD	12.1	12.2
	Post TRT, Mean	71.6	71.8
	Post TRT, SD	7.8	8.6
	FU, Mean	74.5	75.0
	FU, SD	10.3	10.7
BP, Systolic	BSL, Mean	134.3	134.3
(mm Hg)	BSL, SD	19.2	19.8
	IV TRT, Mean	135.1	133.0
	IV TRT, SD	20.9	21.4
	Post TRT, Mean	131.9	132.5
	Post TRT, SD	15.8	16.3
	FU, Mean	128.0	129.6
	FU, SD	18.7	17.1
Temperature	BSL, Mean	36.6	36.6
(degree ºC)	BSL, SD	0.5	0.5
	IV TRT, Mean	36.7	36.7
	IV TRT, SD	0.6	0.7
	Post TRT, Mean	37.4	37.5
	Post TRT, SD	0.8	1.1
	FU, Mean	36.6	36.6
	FU, SD	0.5	0.5
Respiratory Rate	BSL, Mean	17.8	17.8
(rate/min)	BSL, SD	2.1	2.2
	IV TRT, Mean	18.0	18.1
	IV TRT, SD	2.4	2.3
	Post TRT, Mean	18.7	18.8
	Post TRT, SD	1.4	1.4
	FU, Mean	17.9	17.7
	FU, SD	2.2	2.4
BSL=baseline visit, IV TRT=during IV infusion, Post TRT=postoperative period, FU=follow-up assessment visit			
¥Patients may have had more han one vital sign measurement at each of the time points.			

<u>Medical Officer's comment</u>: The M.O. did not note any clinically significant differences in vital signs between the two treatment groups. Therefore, no drug-induced vital sign alterations were detected.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations of vital signs were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not a component of the protocol for the current Study 039. Please refer to the clinical review of the original NDA for additional information.

As part of a Phase 4 commitment, the Applicant submitted a final study report of a Phase 1 protocol examining the effects of a single 2 gram IV dose of ertapenem on the QTc interval in healthy subjects (the approved dose of ertapenem is 1 gram daily). Based on the results of the Phase 1 study and the studies used to support the original NDA, as well as the fact that delayed repolarization has not been recognized in association with administration of other carbapenems or other β-lactam antimicrobials, the Division did not note a need for specific text in the ertapenem label regarding QT prolongation or an increased risk of ventricular arrhythmias in association with this product.

7.1.10 Immunogenicity

Immunogenicity was explored in the original NDA approved November 21, 2001. Please refer to the original clinical review of NDA 21-337 for additional information.

7.1.11 Human Carcinogenicity

Human carcinogenicity was explored in the original NDA approved November 21, 2001. Please refer to the original clinical review of NDA 21-337 for additional information.

7.1.12 Special Safety Studies

As was stated in section 7.1.9, the Applicant performed a Phase 1 study examining the effects of a single 2 gram IV dose of ertapenem on the QTc interval in healthy subjects (the approved dose of ertapenem is 1 gram daily). Based on the results of the Phase 1 study and the studies used to support the original NDA, as well as the fact that delayed repolarization has not been recognized in association with administration of other carbapenems or other β-lactam antimicrobials, the Division did not note a need for specific text in the ertapenem label regarding QT prolongation or an increased risk of ventricular arrhythmias in association with this product.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena and abuse potential were explored in the original NDA approved November 21, 2001. Please refer to the original clinical review of NDA 21-337 for additional information.

7.1.14 Human Reproduction and Pregnancy Data

Effects on human reproduction and pregnancy were explored in the original NDA approved November 21, 2001. Please refer to the original clinical review of NDA 21-337 for additional information.

7.1.15 Assessment of Effect on Growth

Not applicable to this adult single dose prophylaxis supplement to NDA 21-337.

7.1.16 Overdose Experience

In Study 039, all 476 patients exposed to ertapenem received a single 1 gram dose. In the cefotetan arm, 475 patients received a single 2 gram dose of cefotetan. One patient (Patient 2396 at site 024) randomized to the cefotetan arm received two doses of cefotetan.

Medical Officer's comments: ***The Applicant stated on page 42 of the CSR that,***

"Because this study was a single dose study, no dose adjustment was required for patients with renal insufficiency."

The M.O. notes in the ertapenem product label that for other indications, the recommended daily dose of ertapenem for patients with a creatinine clearance ≤ 30 is 500 mg. Five patients (Patient-study site: 2061-003, 2008-005, 2261-034, 2967-036, and 2721-059) treated with ertapenem had a creatinine clearance ≤ 30 at the time of drug infusion. All 5 of these ertapenem patients were women who ranged in age from 71 to 89 years. All of these patients experienced multiple adverse events ranging in number from 5 to 26 adverse experiences per patient. All of these patients had multiple co-morbid conditions that included, but were not limited to hypothyroidism, pulmonary hypertension, coronary artery disease, hypertension, colonic malignant neoplasms, chronic obstructive pulmonary disease, and renal insufficiency. All of these patients were on multiple medications prior to hospitalization and during the perioperative and postoperative periods of hospitalization. None of the adverse events were considered drug-related by investigators. The M.O. noted that two of the patients (2967-036 and 2721-059) experienced confusion as an adverse event during the postoperative hospitalization period. The M.O. noted that both patients had received opiates prior to the reports of confusion. While the M.O. cannot rule out that ertapenem may have played a role in some of the adverse events experienced by these patients, the M.O. noted that all of these patients had multiple reasons for their adverse events as delineated in the preceding discussion. Therefore, for patients with a creatinine clearance ≤ 30, the M.O. concurs that when using ertapenem as a one-time dose for prophylaxis against surgical site infection in elective colorectal surgery patients, no dose adjustment should be made.

Patient 2396 at site 024 received two doses of cefotetan and experienced 7 adverse events (total serum protein decreased, blood albumin decreased, red blood cell count decreased, hemoglobin decreased, hematocrit decreased, nausea, and gastrointestinal pain. All of these

adverse events may have been due to the surgery and underlying medical illness. It is unlikely that any of these adverse events were directly related to study drug therapy.

7.1.17 Postmarketing Experience

As a result of two postmarketing reports on anaphylaxis including anaphylactoid reactions and three postmarketing reports on hallucinations, the following was added to the *Post-Marketing Experience* subsection of the ADVERSE REACTIONS section of the label on April 30, 2004: "The following post-marketing adverse experiences have been reported: *Immune System:* anaphylaxis including anaphylactoid reactions, *Nervous System & Psychiatric:* hallucinations." The Office of Drug Safety was involved with this postmarketing safety assessment and provided one of the "anaphylaxis including anaphylactoid reactions" safety reports.

Since April 30, 2004, no additional postmarketing safety reports have warranted additional changes to the ADVERSE REACTIONS section of the ertapenem label.

7.2 Adequacy of Patient Exposure and Safety Assessments

The dose used in Study 039 was 1 gram given intravenously. The 1 gram dose was approved in the original NDA. This study provided adequate patient exposure and safety assessments for this single dose indication of prophylaxis against surgical site infection in elective colorectal surgery patients.

Animal testing, metabolic testing, and in vitro studies of drug-drug interaction were performed and reviewed during the original NDA. The Applicant provided data on ECG testing to fulfill a Phase 4 commitment associated with the original NDA.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The dose used in Study 039 was 1 gram given intravenously. This is the dose approved in the original NDA. This study provided adequate patient exposure and safety assessments for this single dose indication of prophylaxis against surgical site infection in elective colorectal surgery patients.

The safety dataset for this sNDA was based on the safety analysis set in Study 039. Study 039 was a multicenter, randomized, controlled study. It included all patients who received at least one dose of study drug. In this trial, 476 patients received a single dose of ertapenem and 476 patients received a single dose of cefotetan.

Table 37. Listing of Safety Dataset					
Study Number	**Population**	**Test Drugs**	**Patient Enrollment**	**Mean Duration of Exposure (Days)**	**Range of Exposure (Days)**
039	Elective colorectal surgery patients	Ertapenem 1 gm x 1 dose	500	1	1
		Cefotetan 2 gm x 1 dose	502	1	1

Adverse events were recorded during the preoperative period, on the day of surgery, daily during the postoperative hospitalization period, on the day of hospital discharge, during the 14-day post therapy phone call (if the patient was already discharged), and at the 4-week follow-up visit. Laboratory testing of hematologic status and renal and hepatic function was performed within 30 days prior to study therapy, 48 hours prior to surgery, at least once post-operatively at Day 3-4 (or earlier if patient was to be discharged before Day 3-4) and as clinically indicated, and at the 4-week follow-up visit if clinically indicated.

7.2.1.2 Demographics

The general demographic characteristics of the treated populations in Study 039 follow.

Table 38. Baseline Patient Characteristics by Treatment Group (Treated Population) (adapted from Applicant's Table 6-7, p 69)						
	Ertapenem		**Cefotetan**		**Total**	
	(N=476)		**(N=476)**		**(N=952)**	
	n	(%)	n	(%)	n	(%)
Gender						
Female	204	(42.9)	213	(44.7)	417	(43.8)
Male	272	(57.1)	263	(55.3)	535	(56.2)
Race						
Asian	9	(1.9)	13	(2.7)	22	(2.3)
Black	49	(10.3)	62	(13.0)	111	(11.7)
Hispanic	41	(8.6)	36	(7.6)	77	(8.1)
White	377	(79.2)	362	(76.1)	739	(77.6)
Other	0	(0.0)	3	(0.6)	3	(0.3)
Age (Years)						
18 to 40	35	(7.4)	44	(9.2)	79	(8.3)
41 to 64	227	(47.7)	235	(49.4)	462	(48.5)
65 to 74	122	(25.6)	124	(26.1)	246	(25.8)
>74	92	(19.3)	73	(15.3)	165	(17.3)
Mean	61.6		60.3		60.9	
SD	13.96		13.93		13.96	
Median	63		61		62	
Range	23 to 92		21 to 94		21 to 94	

SD = Standard Deviation

Table 39. Summary of Surgical Procedures by Treatment Group (Treated Population) (modified from Applicant's Table 6-11, p 73-75)

	Ertapenem		Cefotetan		Total	
	(N=476)		(N=476)		(N=952)	
	n	(%)	n	(%)	n	(%)
Stratum						
Intraperitoneal	339	(71.2)	361	(75.8)	700	(73.5)
Abdominoperineal	132	(27.7)	111	(23.3)	243	(25.5)
Bowel Preparation						
No preparation	3	(0.6)	4	(0.8)	7	(0.7)
Polyethylene glycol solution	196	(41.2)	187	(39.3)	383	(40.2)
Polyethylene glycol solution with bisacodyl	18	(3.8)	16	(3.4)	34	(3.6)
Sodium phosphate solution	253	(53.2)	264	(55.5)	517	(54.3)
Not specified	1	(0.2)	1	(0.2)	2	(0.2)
Procedure						
Appendectomy	10	(2.1)	11	(2.3)	21	(2.2)
Biopsy liver	9	(1.9)	9	(1.9)	18	(1.9)
Cecectomy	8	(1.7)	13	(2.7)	21	(2.2)
Cholecystectomy	10	(2.1)	10	(2.1)	20	(2.1)
Colectomy	80	(16.8)	81	(17.0)	161	(16.9)
Colectomy partial	58	(12.2)	62	(13.0)	120	(12.6)
Hemicolectomy	137	(28.8)	150	(31.5)	287	(30.1)
Rectopexy	8	(1.7)	5	(1.1)	13	(1.4)
Resection of rectum	132	(27.7)	111	(23.3)	243	(25.5)
Salpingo-oophorectomy, bilateral	6	(1.3)	4	(0.8)	10	(1.1)
Sigmoidectomy	202	(42.4)	170	(35.7)	372	(39.1)
Small intestinal resection	5	(1.1)	2	(0.4)	7	(0.7)
Transverse colectomy	7	(1.5)	11	(2.3)	18	(1.9)
Other	69	(14.5)	61	(12.8)	130	(13.7)
Primary Diagnosis						
Benign colonic neoplasm	4	(0.8)	14	(2.9)	18	(1.9)
Bowel motility disorder	7	(1.5)	14	(2.9)	21	(2.2)
Colitis ulcerative	11	(2.3)	15	(3.2)	26	(2.7)
Colon adenoma	10	(2.1)	6	(1.3)	16	(1.7)
Colon cancer	217	(45.6)	206	(43.3)	423	(44.4)
Colonic polyp	18	(3.8)	23	(4.8)	41	(4.3)
Colonic stricture	0	(0.0)	6	(1.3)	6	(0.6)
Crohn's disease	7	(1.5)	2	(0.4)	9	(0.9)

Table 39. Summary of Surgical Procedures by Treatment Group (Treated Population) (cont'd) (modified from Applicant's Table 6-11, p 73-75)

	Ertapenem		Cefotetan		Total	
	(N=476)		(N=476)		(N=952)	
	n	(%)	n	(%)	n	(%)
Primary Diagnosis (cont'd)						
Diverticulitis intestinal	50	(10.5)	59	(12.4)	109	(11.4)
Familial adenomatous polyposis	2	(0.4)	5	(1.1)	7	(0.7)
Fistula	5	(1.1)	5	(1.1)	10	(1.1)
Rectal cancer	106	(22.3)	88	(18.5)	194	(20.4)
Rectal prolapse	14	(2.9)	8	(1.7)	22	(2.3)
Other	20	(4.2)	21	(4.4)	41	(4.3)
Duration of Surgery						
Duration ≤ 3.5 hours	393	(82.6)	397	(83.4)	790	(83.0)
Duration > 3.5 hours	78	(16.4)	75	(15.8)	153	(16.1)
Mean (SD) (min)	144.2 (72.3)		146.9 (75.1)		145.6 (73.7)	
N	471		472		943	
Median (min)	130.0		131.5		131.0	
Range (min)	15 to 434		9 to 518		9 to 518	
Time from Study Medication to Skin Incision						
Time ≤ 2 hours	453	(95.2)	444	(93.3)	897	(94.2)
Time > 2 hours	18	(3.8)	28	(5.9)	46	(4.8)
Mean (SD) (min)	61.8 (31.9)		62.4 (34.3)		62.1 (33.1)	
N	471		472		943	
Median (min)	58.0		56.0		57.0	
Range (min post-dosing to skin incision)	-242 to 215		-32 to 265		-242 to 265	

% = (n/Number of Patients Treated) x 100
SD = Standard Deviation
All procedures, primary diagnoses, and additional surgical findings with an incidence > 1% in either treatment are listed in the tables. All items with an incidence < 1% in bo h treatment groups were consolidated into the "other " category.
Patients could have multiple procedures, additional surgical findings, and procedure requirements.
The mean, median, and range for duration of surgery and time from study medica ion to skin incision are calculated in minutes.
Two (2) patients (AN 2188 and AN 2717) in the ertapenem group and two patients in the cefotetan group (AN 2272 and AN 2726) received study medication after skin incision. Therefore, the range of time from study medication to skin incision is shown as a negative number.
Four patients (AN 2005, AN 2098, AN 2710, AN 2968) in the ertapenem group and four patients (AN 2332, AN 2388, AN 2423, AN 3753) in the cefotetan group were treated but did not have surgery. One patient (AN 2522) in the ertapenem group had surgery performed but the surgical source documentation was lost. Baseline surgical information was not provided for these patients and they are not included in the summary.

Table 40. Risk Factors for Post-Operative Infection by Treatment Group (Treated Population) (adapted from Applicant's Table 6-15, p 82)

	Ertapenem		Cefotetan		Total	
	(N=476)		(N=476)		(N=952)	
	n	(%)	n	(%)	n	(%)
Tobacco Use						
Non-user	233	(48.9)	218	(45.8)	451	(47.4)
Current user	98	(20.6)	102	(21.4)	200	(21.0)
Ex-user	145	(30.5)	153	(32.1)	298	(31.3)
Not specified	0	(0.0)	3	(0.6)	3	(0.3)
BMI (kg/m^2)						
Mean (SD)	27.7	(5.9)	27.9	(6.2)	27.8	(6.0)
N	455		461		916	
Median	27		27.3		27.1	
Range	12.3 to 54.8		13.7 to 63.6		12.3 to 63.6	
Creatinine Clearance ($mL/min/1.73m^2$)						
> 30	451	(94.7)	451	(94.7)	902	(94.7)
≤ 30	5	(1.1)	8	(1.7)	13	(1.4)
Not specified	20	(4.2)	17	(3.6)	37	(3.9)
Obesity (BMI > 30 kg/m^2)						
	135	(28.4)	140	(29.4)	275	(28.9)
Diabetes						
	85	(17.9)	87	(18.3)	172	(18.1)
Albumin (Baseline Albumin ≤ 2 g/dL)						
	1	(0.2)	6	(1.3)	7	(0.7)

Creatinine Clearance calculation: Men=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL), Women=(140-age (yrs))*weight (kg)/72*serum creatinine (mg/dL)*0.85
%=(n/Number of Patients Treated)*100
BMI was not calculated for 21 patients (ANs 2429, 2466, 2659, 2405, 2342, 2401, 2522, 2103, 2781, 2805, 2806, 2841, 2897, 2610, 2653, 2741, 2793, 2796, 2832, 3731, 3749) in the ertapenem group and 15 patients (ANs 2201, 2248, 2872, 2898, 2899, 2398, 2655, 2794, 2830, 2894, 2895, 3654, 3656, 3698, 2640) in the cefotetan group where height and/or weight were not provided.

Medical Officer's comment: In general, demographic characteristics in the treated population were evenly distributed between groups, including strata of surgical procedures and risk factors for post-operative infection.

7.2.1.3 Extent of exposure (dose/duration)

In this trial, 476 patients received a single dose of ertapenem and 475 patients received a single dose of cefotetan. One patient (Patient 2396 at site 024) randomized to the cefotetan arm received two doses of cefotetan.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No additional studies were submitted or reviewed to evaluate the safety of this drug product in relation to prophylaxis against surgical site infection in elective colorectal surgery patients.

7.2.2.2 Postmarketing experience

Please refer to section 7.1.17 of this review for additional information on postmarketing experience with ertapenem.

7.2.2.3 Literature

The Applicant's current submission did not contain literature references that spoke to the safety profile of ertapenem. Please refer to the clinical reviews of the original NDA 21-337 submission and supplement for the diabetic foot infection sub-indication for commentary on previously submitted literature references on ertapenem's safety profile.

Medical Officer's comments: The Medical Officer found the following recent reference that comments on the safety profile of ertapenem in surgical patients.

Dela Pena AS, Asperger W, Kockerling F, Raz R, Kafka R, Warren B, Shivaprakash M, Vrijens F, Giezek H, Dinubile MJ, Chan CY; for the Optimizing Intra-Abdominal Surgery with Invanz (OASIS)-I Study Group. Efficacy and Safety of Ertapenem Versus Piperacillin-Tazobactam for the Treatment of Intra-Abdominal Infections Requiring Surgical Intervention. J Gastrointest Surg. 2006 Apr;10(4):567-574.[8]

The Medical Officer reviewed this reference. It was co-authored by Applicant employees. The safety information provided in this paper is consistent with the current product labeling of ertapenem.

7.2.3 Adequacy of Overall Clinical Experience

Within the context of a single 1 gram dose of ertapenem for prophylaxis against surgical site infection in elective colorectal surgery patients, the extent and duration of exposure needed to assess safety was adequate. Study 039 was not intended to assess the safe use of ertapenem for prophylaxis against surgical site infection in any other types of surgical procedures or patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable for this sNDA. No additional special animal or in vitro testing was performed for this sNDA.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of patients with regard to monitoring laboratory parameters, vital signs, and efforts to elicit adverse events was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable. Please refer back to the original clinical review of NDA 21-337.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant adequately evaluated patients for potential drug class-related adverse events, including, but not limited to ascertaining for episodes of *Clostridium difficile* infection and colitis, seizure, worsening renal dysfunction, liver dysfunction, and neutropenia. Please refer to the original clinical review of NDA 21-337 for additional information.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the data available for conducting the safety review was adequate.

7.2.9 Additional Submissions, Including Safety Update

On January 20, 2006, the Applicant submitted a Periodic Adverse Experience Report for ertapenem for the time period from November 22, 2004 through November 21, 2005.

No additional safety update is required in the proposed label.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 *Clostridium difficile* infection or colitis

Eight (1.7%) ertapenem patients and 3 (0.6%) cefotetan patients developed *Clostridium difficile* infection or colitis. Investigators attributed that the *Clostridium difficile* infection or colitis was drug-related in 5 of the ertapenem patients and in 1 of the cefotetan patients. The M.O. noted that none of the other ertapenem or cefotetan patients were exposed to additional antibacterial agents prior to the development of *Clostridium difficile* infection or colitis. Therefore, the M.O. considered all of the adverse events of *Clostridium difficile* infection or colitis to be drug-related, i.e., 8 (1.7%) ertapenem patients and 3 (0.6%) cefotetan patients.

Please refer to section 7.1.5 for additional details and analyses.

Medical Officer's comment: Upon review of the current product label for ertapenem, the Medical Officer notes that "C. difficile associated diarrhea" was reported with an overall incidence of >0.1%. This is appropriate given the overall experience of ertapenem in Phase 2 and 3 clinical studies. (b) (4)

(b) (4)

[redacted]

Please refer to section 7.1.5 for additional details.

7.3.2 Seizures

No patients on ertapenem developed a seizure during study therapy or the 4 week follow-up period.

Medical Officer's comment: Upon review of the current product label for ertapenem, the Medical Officer notes that seizure was reported in 0.5% of ertapenem patients in prior clinical studies. Given the sample size of patients in this study, an absence of drug-related seizure is not inconsistent with the current product labeling.

7.3.3 Neutropenia

In the ertapenem group, 2/396 patients had an absolute neutrophil count less than 1800/microL, and no ertapenem patients had an absolute neutrophil count less than 1000/microL. Neither of these patients' low neutrophil counts was reported as adverse events. After review of the patients' CRFs, the Medical Officer cannot rule out the possibility that ertapenem contributed to the low neutrophil counts. Please refer to section 7.1.7.5 for additional details and analyses.

Medical Officer's comment: Upon review of the current product label for ertapenem, the Medical Officer notes that "segmented neutrophils decreased" was reported in ≥ 1% of ertapenem patients in prior clinical studies. Given the sample size of patients in this study, the rate of potentially drug-related and clinically significant decline in segmented neutrophils is not inconsistent with the current product labeling.

7.3.4 Renal Dysfunction

No patients in either treatment group were reported as having drug-related renal dysfunction. Three out of 449 (0.7%) of ertapenem patients had increases in serum creatinine to > 1.5 times the upper limit of normal (ULN). After review of the patients' CRFs, the Medical Officer cannot rule out the possibility that ertapenem may have contributed to the increases in serum creatinine. Please refer to section 7.1.7.5 for additional details and analyses.

Medical Officer's comment: Upon review of the current product label for ertapenem, the Medical Officer notes that "serum creatinine increased" was reported in ≥ 1% of ertapenem

patients in prior clinical studies. The rate of drug-related increase in blood creatinine found in this study is consistent with current product labeling.

7.3.5 Elevated liver enzyme studies

One (0.2%) ertapenem patient and 3 (0.6%) cefotetan patients developed drug-related increases in ALT. One (0.2%) ertapenem patient and 2 (0.4%) cefotetan patients developed drug-related increases in AST. No patients developed drug-related increases in alkaline phosphatase. No ertapenem patients and 1 (0.2%) cefotetan patient developed a drug-related increase in total and direct bilirubin.

In addition, 10 (2.5%) ertapenem patients had an increase in total serum bilirubin to > 2.5 x ULN. However, most of these patients had pre-existing hepatobiliary disease and were exposed to potentially hepatotoxic drugs during the perioperative and postoperative periods of hospitalization. It was therefore difficult to attribute these elevations in bilirubin to a single 1 gram dose of ertapenem.

Please refer to sections 7.1.5, 7.1.7.3, and 7.1.7.5 for additional details and analyses.

Medical Officer's comment: Upon review of the current product label for ertapenem, the M.O. notes that in prior clinical studies patients had the following drug-related liver enzyme elevations: 6.0% had increased ALT, 5.2% had increased AST, and 3.4% had increase alkaline phosphatase. Given the sample size of patients in this study, the rate of drug-related elevated liver enzyme studies is not inconsistent with current product labeling.

The current product label contains elevation in serum bilirubin as an adverse event at a frequency of ≥ 1% regardless of attribution to study drug. Currently, this is appropriate given: (1) the overall experience with ertapenem in Phase 2 and 3 studies, (2) most of the patients with elevations in serum bilirubin had hepatobiliary co-morbidity and were exposed to potentially hepatotoxic drugs during the perioperative and postoperative periods of hospitalization, and (3) it was therefore difficult to attribute these elevations in bilirubin to a single 1 gram dose of ertapenem.

7.4 General Methodology

The Medical Officer reviewed the Study 039 safety database for safety signals consistent with the safety section of the current product label for ertapenem. Particular attention was paid to *Clostridium difficile* infection and/or colitis, seizures, renal dysfunction, liver enzyme elevation, neutropenia, as well as all deaths, all drug-induced adverse events, all withdrawals due to drug-related adverse events, and all patients with outlying laboratory abnormalities.

Medical Officer's comment: The M.O. recommends the following changes to the safety section of the label.

1 Page Immediately Following Withheld - b(4) Draft Labeling

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Medical Officer reviewed the safety data only from Study 039. There was no pooling of data from other studies.

7.4.1.2 Combining data

The Medical Officer reviewed the safety data only from Study 039. There was no pooling of data from other studies.

7.4.2 Explorations for Predictive Factors

Please refer to section 7.1.5 for a discussion of predictive factors associated with acquisition of *Clostridium difficile* infection or colitis, including presence of one dose of study drug as the only antibacterial therapy prior to infection or colitis and association with two specific study sites for > 50% of the affected patients.

7.4.3 Causality Determination

Based upon the review of the Study 039 safety database, knowledge of ertapenem's class-specific adverse effects, review of the current ertapenem product label, and of the literature, it is likely that ertapenem may cause *Clostridium difficile* infection or colitis, seizure, neutropenia, renal dysfunction, and elevation in liver enzyme studies. Please refer to the current product labeling for a complete list of drug-related adverse events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Ertapenem is to be given intravenously as a single 1 gram dose in all adult patients, including those with impaired renal function, 60 minutes prior to elective colorectal surgery.

8.2 Drug-Drug Interactions

No new information on drug-drug interactions was submitted or found during the review of this supplemental new drug application.

8.3 Special Populations

The Applicant has not submitted any new information on special populations. For additional details on studies previously performed in special populations, please refer to the original clinical review of NDA 21-337.

8.4 Pediatrics

No new information is included in this submission. On May 18, 2005, the Applicant received Agency approval for use of ertapenem in pediatric patients as young as 3 months old for the treatment of complicated urinary tract infections, skin and soft tissue infections, community-acquired pneumonia, complicated intra-abdominal infections, and acute pelvic infections.

Medical Officer's comment: The Medical Officer believes that it is appropriate to grant a waiver for pediatric studies for this indication based on the following. (1) The Medical Officer believes that the Applicant would have difficulty recruiting an adequate number of pediatric patients because elective colorectal surgeries mainly occur in adult patients. (2) The Applicant has demonstrated adequate safety information for pediatric patients with complicated intra-abdominal infections and complicated skin and skin structure infections in Supplement No. 018. (3) It would be reasonable to extrapolate from the current adult Study 039 and the pediatric Supplement No. 018 that ertapenem would be efficacious for prophylaxis against surgical site infection in pediatric patients undergoing elective colorectal surgeries given the similarity in potential pathogens that may cause surgical site infections in pediatric patients undergoing elective colorectal surgery.

8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee meeting was convened to discuss the contents of this sNDA.

8.6 Literature Review

Literature is referenced throughout this review. Please refer to the References section at the end of this review for a complete listing.

8.7 Postmarketing Risk Management Plan

No additional postmarketing risk management activities are recommended beyond those generally employed for all drug products post-approval.

8.8 Other Relevant Materials

Not applicable. No additional relevant materials were reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

Ertapenem, 1 gram IV as a single dose 1 hour prior to surgery, is safe and effective as prophylaxis against surgical site infections in elective colorectal surgery patients.

9.2 Recommendation on Regulatory Action

This efficacy supplement may be approved.

9.3 Recommendation on Postmarketing Actions

Ertapenem was approved November 21, 2001 in the United States for several indications including complicated intra-abdominal infections and complicated skin and skin structure infections. No changes in current postmarketing reporting requirements are recommended.

9.3.1 Risk Management Activity

The Medical Officer does not recommend any additional postmarketing risk management activities beyond those generally employed for all drug products post-approval.

9.3.2 Required Phase 4 Commitments

The Medical Officer does not recommend a Phase 4 commitment.

9.3.3 Other Phase 4 Requests

The Medical Officer does not recommend a Phase 4 request.

9.4 Labeling Review

The Applicant's proposed labeling is generally acceptable. The following modifications are recommended:

(b) (4)

3 Pages Immediately Following withheld - b(4) Draft Labeling

9.5 Comments to Applicant

1. [redacted] (b) (4)

2. In an exploratory analysis of surgeries lasting longer than 4 hours, ertapenem patients had a prophylactic success rate of 67.1% (49/73) and cefotetan patients had a success rate of 40.6% (26/64). The difference in prophylactic success of 26.5% was more than twice the difference observed in surgeries that lasted < 4 hours (10.3%). The Applicant may consider performing a second adequate and well-controlled clinical trial to confirm this exploratory analysis.

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/s/

Peter Kim
7/25/2006 07:54:47 AM
MEDICAL OFFICER
Recommendations on labeling revisions and additional comments sent to Applicant on 7/24/06.

Peter Kim
7/25/2006 07:56:10 AM
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Jean Mulinde
7/25/2006 10:21:41 AM
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Janice Soreth
7/25/2006 04:39:34 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-337 / S021
Drug Name:	Invanz® (Ertapenem for injection)
Indication(s):	Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery
Applicant:	Merck
Date(s):	Submitted: 11/09/05
PDUFA Date:	09/08/2006
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Yunfan Deng, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmologic Drug Products (HFD-520)
Clinical Team:	Peter Kim, M.D, Medical Reviewer Jean Mulinde, M.D, Medical Team Leader
Project Manager:	Susmita Samanta, M.D

Keywords:

NDA, one study application

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LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review focused on the efficacy of INVANZ® (Ertapenem Sodium) for the prophylaxis of surgical site infection following elective colorectal surgery. In study 039, Ertapenem demonstrated non-inferiority to Cefotetan using a margin of 10% with respect to clinical favorable response rates for the prophylaxis of surgical site infection following elective colorectal surgery. In the EPP population, the clinical favorable response rate of Ertapenem vs. Cefotetan was 70.6% vs. 57.3%, a 13.3% treatment difference with 95% confidence interval of (6.1%, 20.4%); and in the MITT population, the corresponding rates were: 58.4% vs. 48.8%, a 9.6% treatment difference with 95% confidence interval of (2.9%, 15.9%). For both Ertapenem and Cefotetan groups, observed cure rates in the MITT population were lower compared to the EPP population.

1.2 Brief Overview of Clinical Studies

This submission contains one efficacy/safety study. This study (Protocol 039) is a prospective, multicenter, double-blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of a single dose of Ertapenem Sodium versus Cefotetan for the prophylaxis of surgical site infection following elective colorectal surgery.

The primary objective is to compare the efficacy of ertapenem sodium with that of Cefotetan in the prophylaxis of surgical site infection following elective colorectal surgery.

1.3 Statistical Issues and Findings

The sponsor considered evaluable per-protocol (EPP) analysis as the primary analysis population and considered the modified intent-to-treat (MITT) analyses as supportive of the respective evaluable patient analysis. However, in non-inferiority trials, both analyses can potentially bias the results. Therefore, the primary analyses would be based on MITT and EPP as co-primary populations.

The EPP population is the population comprised of patients who received a complete dose of prophylaxis no more than two hours prior to initial surgical incision and no more than six hours before surgical closure, who have had primary skin closure, and in whom sufficient information was available to determine the outcome of prophylaxis at the 4-week follow-up assessment with no confounding factors present that interfered with that assessment (e.g. other systemic antibiotics or other prophylactic use of an anti-infective agent not allowed by protocol such as antibiotic in lavage fluid).

The modified intent-to-treat (MITT) population is the population comprised of all patients randomized and treated, who had elective open surgery of the colon or rectum with completion of mechanical bowel preparation procedure and who received a complete dose of study medication at any time before or during surgery.

Generally, two adequate and well-controlled studies, each convincing on its own, would provide substantial evidence of efficacy and safety. The need for more than one study is based upon the scientific principle of replication of study results to ensure that the results of a single study are more than a chance occurrence. However, this drug has been approved for other indications and based on earlier discussions with the agency, it was agreed that one study should be adequate for this indication.

2. INTRODUCTION

2.1 Overview

Ertapenem is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics. It is currently approved in adults for the treatment of the following diseases: CAP, complicated UTI including Pyelonephritis, cSSSI, complicated IA1, and API. The Sponsor proposes to extend the use of ertapenem for the prophylaxis of surgical site infection following elective colorectal surgery.

This submission has one efficacy/ safety studies. The study (Protocol 039) is a prospective, multicenter, double-blind, randomized, comparative study to evaluate the safety, efficacy, and tolerability of Ertapenem Sodium versus Cefotetan for prophylaxis of surgical site infection following elective colorectal surgery.

2.2 Data Sources

The Sponsor's study reports for study 039 are available on the EDR at
\\Cdsesub1\evsprod\n021337

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The primary objective of the study was to compare the efficacy of Ertapenem Sodium with that of Cefotetan in the prophylaxis of surgical site infection following elective colorectal surgery. The Protocol 039 was designed to demonstrate non-inferiority of the Ertapenem group to the comparator group for this indication. Ertapenem was considered non-inferior to Cefotetan if the 95% (two-sided) CI for the difference in response rates between two treatment groups contained zero and the lower limit of the CI was greater than -10%.

Objectives

Primary: To compare the efficacy of Ertapenem Sodium with that of Cefotetan in the prophylaxis of surgical site infection following elective colorectal surgery.
Secondary: (1) To document the microbiology of surgical site infections in patients who fail prophylaxis and/or who have distant site infection. (2) To evaluate and compare the safety profile of Ertapenem Sodium versus Cefotetan with respect to the proportion of patients with any drug-related adverse experiences (AEs).

3.1.1 Study Design and Endpoints

Protocol 039 was a randomized, multicenter, double-blind study comparing Ertapenem Sodium 1g IV with Cefotetan 2g IV for the prophylaxis of surgical site infection following elective colorectal surgery in patients ≥ 18 years of age. The study involved 1001 patients.

Patients were randomized to one of the two study treatments in a 1:1 ratio at study entry. Patients were stratified by pre-specified planned surgical procedures; stratum I being those patients with a planned intraperitoneal procedure, and stratum II being those patients planned to have an abdominoperineal resection. The primary endpoint is the proportion of patients with a favorable clinical outcome at the time of follow-up (4 weeks post-treatment) visit.

The EPP population is comprised of patients who received a complete dose of prophylaxis no more than two hours prior to initial surgical incision and no more than six hours before surgical closure, who have had primary skin closure, and in whom sufficient information was available to determine the outcome of prophylaxis at the 4-week follow-up assessment with no confounding factors present that interfered with that assessment (e.g. other systemic antibiotics or other prophylactic use of an anti-infective agent not allowed by protocol such as antibiotic in lavage fluid).

The modified intent-to-treat (MITT) population is the population comprised of all patients randomized and treated, who had elective open surgery of the colon or rectum with completion of mechanical bowel preparation procedure and who received a complete dose of study medication at any time before or during surgery. The analyses of the MITT population and the EPP population were co-primary analyses.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 1: Patient Disposition

	Ertapenem	Cefotetan	Total
Patient Randomized	500	502	1002
Randomized not treated	24	26	50
Patients treated	476	476	952
Patients completed	450	441	891
Patients discontinued:	26	35	61
Clinical adverse experience	11	10	21
Lost to follow-up	3	9	12
Withdrew consent	1	1	2
Protocol deviation	11	15	26
Patients deemed EPP	346	339	685
Patients deemed MITT	451	450	901
From sponsor's Table 6-1 of Clinical Study Report (CSR), p 59			

One thousand and two (1002) patients were randomized into the study, with 952 patients receiving treatment from a total of 51 study sites in the United States. There were 346/476 (72.7%) of the treated patients in the Ertapenem group and 339/476 (71.2%) treated patients in

the Cefotetan group who were evaluable per-protocol (EPP) for the primary analyses. The MITT population included 451/500 (90.2%) of the patients randomized to the ertapenem group and 450/502 (89.6%).

Table 2: Demographics (Treated Population)

		Ertapenem (N=476)		Cefotetan (N=476)		Total (N=952)	
		n	(%)	n	(%)	n	(%)
Gender	Female	204	(42.9)	213	(44.7)	417	(43.8)
	Male	272	(57.1)	263	(55.3)	535	(56.2)
Age	17 And Under	0	(0.0)	0	(0.0)	0	(0.0)
	18 to 40	35	(7.4)	44	(9.2)	79	(8.3)
	41 to 64	227	(47.7)	235	(49.4)	462	(48.5)
	65 to 74	122	(25.6)	124	(26.1)	246	(25.8)
	Over 74	92	(19.3)	73	(15.3)	165	(17.3)
	MEAN		61.6		60.3		60.9
	SD		13.96		13.93		13.96
	MEDIAN		63.0		61.0		62.0
	RANGE		23 to 92		21 to 94		21 to 94
Race	Asian	9	(1.9)	13	(2.7)	22	(2.3)
	Black	49	(10.3)	62	(13.0)	111	(11.7)
	Hispanic American	41	(8.6)	36	(7.6)	77	(8.1)
	Other	0	(0.0)	3	(0.6)	3	(0.3)
	White	377	(79.2)	362	(76.1)	739	(77.6)
From sponsor's Table 6-7 of CSR, p 69							

Table 3: Demographics (Evaluable Population)

		Ertapenem (N=346)		Cefotetan (N=339)		Total (N=685)	
		n	(%)	n	(%)	n	(%)
Gender	Female	153	(44.2)	160	(47.2)	313	(45.7)
	Male	193	(55.8)	179	(52.8)	372	(54.3)
Age	17 And Under	0	(0.0)	0	(0.0)	0	(0.0)
	18 to 40	24	(6.9)	36	(10.6)	60	(8.8)
	41 to 64	171	(49.4)	158	(46.6)	329	(48.0)
	65 to 74	89	(25.7)	93	(27.4)	182	(26.6)
	Over 74	62	(17.9)	52	(15.3)	114	(16.6)
	MEAN		61.3		60.0		60.7
	SD		13.68		14.42		14.06
	MEDIAN		63.0		62.0		62.0
	RANGE		23 to 92		21 to 94		21 to 94
Race	Asian	8	(2.3)	9	(2.7)	17	(2.5)
	Black	40	(11.6)	46	(13.6)	86	(12.6)
	Hispanic American	26	(7.5)	24	(7.1)	50	(7.3)
	Other	0	(0.0)	3	(0.9)	3	(0.5)
	White	272	(78.6)	257	(75.8)	529	(77.2)
Modified from sponsor's Table 6-8 of CSR, p 70							

Table 4 Baseline Characteristics (MITT Population)

	Ertapenem		Cefotetan		Total	
	(N=451)		(N=450)		(N=901)	
	n	(%)	n	(%)	n	(%)
Stratum						
Intraperitoneal	330	(73.2)	346	(76.9)	676	(75.0)
Abdominoperineal	121	(26.8)	104	(23.1)	225	(25.0)
Bowel Preparation						
No preparation	0	(0.0)	0	(0.0)	0	(0.0)
Polyethylene glycol solution	189	(41.9)	177	(39.3)	366	(40.6)
Polyethylene glycol solution with bisacodyl	16	(3.6)	15	(3.3)	31	(3.4)
Sodium phosphate solution	245	(54.3)	257	(57.1)	502	(55.7)
Not specified	1	(0.2)	1	(0.2)	2	(0.2)
Surgical Procedure						
Appendectomy	9	(2.0)	11	(2.4)	20	(2.2)
Biopsy liver	9	(2.0)	9	(2.0)	18	(2.0)
Caecectomy	7	(1.6)	13	(2.9)	20	(2.2)
Cholecystectomy	10	(2.2)	10	(2.2)	20	(2.2)
Colectomy	80	(17.7)	78	(17.3)	158	(17.5)
Colectomy partial	57	(12.6)	61	(13.6)	118	(13.1)
Hemicolectomy	134	(29.7)	147	(32.7)	281	(31.2)
Ileectomy	3	(0.7)	4	(0.9)	7	(0.8)
Rectopexy	8	(1.8)	5	(1.1)	13	(1.4)
Resection of rectum	121	(26.8)	104	(23.1)	225	(25.0)
Salpingo-oophorectomy, bilateral	5	(1.1)	4	(0.9)	9	(1.0)
Sigmoidectomy	200	(44.3)	167	(37.1)	367	(40.7)
Small intestinal resection	5	(1.1)	1	(0.2)	6	(0.7)
Transverse colectomy	7	(1.6)	11	(2.4)	18	(2.0)
Other	58	(12.9)	51	(11.3)	109	(12.1)
Primary Diagnosis						
Benign colonic neoplasm	4	(0.9)	14	(3.1)	18	(2.0)
Bowel motility disorder	7	(1.6)	14	(3.1)	21	(2.3)

Colitis ulcerative	10	(2.2)	15	(3.3)	25	(2.8)
Colon adenoma	10	(2.2)	6	(1.3)	16	(1.8)
Colon cancer	214	(47.5)	199	(44.2)	413	(45.8)
Colonic polyp	18	(4.0)	23	(5.1)	41	(4.6)
Colonic stricture	0	(0.0)	6	(1.3)	6	(0.7)
Crohn's disease	6	(1.3)	2	(0.4)	8	(0.9)
Diverticulitis intestinal	49	(10.9)	55	(12.2)	104	(11.5)
Familial adenomatous polyposis	2	(0.4)	5	(1.1)	7	(0.8)
Fistula	4	(0.9)	4	(0.9)	8	(0.9)
Rectal cancer	97	(21.5)	80	(17.8)	177	(19.6)
Rectal prolapse	14	(3.1)	8	(1.8)	22	(2.4)
Other	16	(3.5)	19	(4.2)	35	(3.9)
Duration of Surgery						
Duration $\leq$ 3.5 hours	377	(83.6)	384	(85.3)	761	(84.5)
Duration > 3.5 hours	74	(16.4)	66	(14.7)	140	(15.5)
Mean (SD) (min)	143.5 (71.1)		143.8 (71.7)		143.6 (71.4)	
N	451		450		901	
Median (min)	130.0		130.0		130.0	
Range (min)	15 to 432		9 to 518		9 to 518	
Time from Study Medication to Skin Incision						
Mean (SD) (min)	62.1 (32.2)		62.3 (34.0)		62.2 (33.1)	
N	451		450		901	
Median (min)	58.0		56.0		57	
Range (min post-dosing to skin incision)	-242 to 215		-32 to 265		-242 to 265	

% = (n/Number of Patients Treated) x 100
SD = Standard Deviation
All procedures, primary diagnoses, and additional surgical findings with an incidence > 1% in either treatment are listed in the tables. All items with an incidence < 1% in both treatment groups were consolidated into the "other " category.
Patients could have multiple procedures, additional surgical findings, and procedure requirements.
The mean, median, and range for duration of surgery and time from study medication to skin incision are calculated in minutes.
From sponsor's Table 6-11 of CSR, p 73

3.1.3 Statistical Methodologies

The co-primary efficacy analyses were performed on both the evaluable patient population and the modified-intent-to-treat population. The primary endpoint of interest was the favorable clinical response rate at the 4-week post-treatment follow-up assessment. Non-inferiority within

a 10% margin was demonstrated using 2-sided 95% confidence interval for the difference in response rates between the treatment groups. The difference in clinical response rate of Ertapenem vs. Cefotetan in the EPP population was 13.3% with 95% CI of (6.1%, 20.4%); and in the MITT population was 9.6% with 95% CI of (2.9%, 15.9%). Patients were stratified by pre-specified planned surgical procedures. The statistical test of treatment by surgical procedure interaction (Breslow-Day Test of Homogeneity of Odds-Rations) was performed, it was not significant. Therefore, these strata were combined for the primary analyses. The confidence interval was adjusted by Cochran-Mantel-Haenszel type weights. Results based on the analyses of the unadjusted observed data were consistent.

Evaluable patients who were clinical failures prior to the 4-week visit were considered failures/unfavorable for all subsequent time points, including the 4-weeks post-treatment follow-up assessment. The modified-intent-to-treat (MITT) analysis considered missing outcomes as unfavorable and was also performed as a co-primary analysis.

3.1.4 Results and Conclusions

For the EPP analysis, 346 out of 476 treated patients (72.7%) in the Ertapenem group and 339 (71.2%) out of 476 treated patients (71.2%) in the Cefotetan group were evaluable. Patients were stratified for balance across the treatment groups at study entry by pre-specified strata -- planned surgical procedures. Stratum I included patients with planned intraperitoneal procedures, Stratum II included patients with planned abdominoperineal resection.

The proportion of patients with a favorable clinical response in the EPP and MITT populations are listed in Table 5, and Table 6 respectively.

Table 5. Proportion of Patients with Favorable Clinical Response Assessment at 4-Weeks Post-Treatment (Evaluable Population)

Treatment Group				
Ertapenem (A)		Cefotetan (B)		
Estimated † Responses				Estimated † Difference (A - B)
n/N	%	n/N	%	% (95% CI)
244/346	70.6	194/339	57.3	13.3 (6.1, 20.4)
Observed Responses				Observed Difference (A - B)
n/N	%	n/N	%	% (95% CI)
244/346	70.5	194/339	57.2	13.3 (6.1, 20.4)

† Percents and 95% Confidence Intervals were adjusted by Cochran-Mantel-Haenszel type weights.

N = Number of evaluable patients in each treatment group.

n = Number of evaluable patients with a favorable clinical response assessment in each treatment group.

CI = Confidence interval.

Modified from Sponsor's Table 7-1, p 99

Table 6. Proportion of Patients With Favorable Clinical Response Assessment at 4-Weeks Post-Treatment (MITT Population)

Treatment Group				
Ertapenem (A)		Cefotetan (B)		
Estimated † Response				Estimated † Difference (A - B)
n/N	%	n/N	%	% (95% CI)
263/451	58.4	220/450	48.8	9.6 (3.1, 16.0)
Observed Response				Observed Difference (A - B)
n	%	n/N	%	% (95% CI)
263/451	58.3	220/450	48.9	9.4 (2.9, 15.9)

† Percents and 95% Confidence Intervals were adjusted by Cochran-Mantel-Haenszel type weights.

N = Number of MITT qualified patients in each treatment group.

n = Number of MITT qualified patients with a favorable clinical response assessment in each treatment group.

CI = Confidence interval.

Modified from Sponsor's Table 11-8, p 423

Statistical Reviewer's Comments:

From these results, Ertapenem has demonstrated evidence of non-inferiority to Cefotetan based on the primary hypothesis.

The proportion of patients with a favorable response stratified by prospectively specified surgical procedures in the EPP and MITT populations are listed in Table 7, and Table 8 respectively. Overall the response rates were similar within treatment groups. The test of treatment by surgical procedure interaction (Breslow-Day Test of Homogeneity of Odds-Rations) was performed and it was not significant. Therefore, the strata were combined for the primary analyses.

Table 7 Analyses of Outcomes by surgical procedure (EPP Population)

	Ertapenem (A) (N=346)		**Cefotetan (B) (N=339)**		**Observed Differences (A-B)**
	Observed Response		**Observed Response**		
Surgical Procedure	n/m	%	n/m	%	%
Intraperitoneal	185/259	71.4	153/270	56.7	14.8
Abdominoperineal	59/87	67.8	41/69	59.4	8.4

N = Number of Evaluable patients in each treatment group.

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

CI = Confidence interval.

Modified from Sponsor's Table 7-2, p 100

Table 8 Analyses of Outcomes by surgical procedure (MITT Population)

	Ertapenem (A) (N=451)		Cefotetan (B) (N=450)		Observed Differences (A-B)
	Observed Response		Observed Response		
Surgical Procedure	n/m	%	n/m	%	%
Intraperitoneal	198/330	60.0	172/346	49.7	10.3
Abdominoperineal	65/121	53.7	48/104	46.2	7.6

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.

Statistical Reviewer's Comments:

The results based on surgical procedures were robust compared to the primary analysis results.

Generally, two adequate and well-controlled studies, each convincing on its own, would provide substantial evidence of efficacy and safety. The need for more than one study is based upon the scientific principle of replication of study results to ensure that the results of a single study are more than a chance occurrence. However, this drug has been approved for other indications and based on earlier discussions with the agency, it was agreed that one study should be adequate for this indication.

3.2 Evaluation of Safety

Overall 738 out of 952 patients (77.5%) experienced clinical adverse experiences during study therapy and 14-day follow-up period (Table 9). There were 31 patients (6.5%) in the ertapenem group and 33 patients (6.9%) in the cefotetan group with drug related adverse experiences; 3 patients (0.6%) in the ertapenem group and 3 patients (0.6%) in the cefotetan group experienced drug related serious adverse experiences. One patient in the cefotetan group discontinued study therapy due to a drug related adverse experience. No patients discontinued due to drug related serious adverse experiences.

Table 9 Clinical Adverse Experience Summary During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=476)		Cefotetan (N=476)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	357	(75.0)	381	(80.0)
With no adverse experience	119	(25.0)	95	(20.0)
With drug-related adverse experiences†	31	(6.5)	33	(6.9)
With serious adverse experiences	98	(20.6)	121	(25.4)
With serious drug-related adverse experiences	3	(0.6)	3	(0.6)
Who died	3	(0.6)	7	(1.5)
Discontinued due to adverse experiences	0	(0.0)	1	(0.2)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(0.2)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.
From sponsor's Table 8-1 of CSR, p 166.

Please see the review of the medical officer Dr. Peter Kim for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The proportion of patients with a favorable response in the EPP and MITT populations by gender, age group, and race are listed in Table 10, and Table 11 respectively.

Table 10 Analyses of Outcomes by gender, age, and race (EPP Population)

	Ertapenem (A) (N=346) Observed Response		Cefotetan (B) (N=339) Observed Response		Observed Differences (A-B)
	n/m	%	n/m	%	%
Gender					
Female	107/153	70.0	100/160	62.5	7.4
Male	137/193	71.0	94/179	52.5	18.5
Age					
< 65 years	134/195	68.7	116/194	59.8	8.9
≥ 65 years	110/151	72.8	78/145	53.8	19.1
< 75 years	197/284	69.4	164/287	57.1	12.2
≥ 75 years	47/62	75.8	30/52	57.7	18.1
Race					
Hispanic	17/26	65.4	10/24	41.7	23.7
Black	27/40	67.5	27/46	58.7	8.8
White	195/272	71.7	148/257	57.6	14.1
Other	5/8	62.5	9/12	75.0	-12.5

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
Modified from Applicant's Table 7-8 of CSR, p 125.

Table 11 Analyses of Outcomes by Gender, Age, and Race (MITT Population)

	Ertapenem (A) (N=451) Observed Response		Cefotetan (B) (N=450) Observed Response		Observed Differences (A-B)
	n/m	%	n/m	%	%
Gender					
Female	125/193	64.8	110/201	59.2	5.6
Male	171/258	66.3	129/249	51.8	14.5
Age					
< 65 years	157/248	63.3	149/265	56.2	7.1
≥ 65 years	139/203	68.5	99/185	53.5	15.0
< 75 years	233/364	64.0	207/380	54.5	9.5
≥ 75 years	63/87	72.4	41/70	58.6	13.8
Race					
Hispanic	21/35	60.0	15/32	46.9	13.1
Black	31/49	63.3	32/57	56.1	7.1
White	238/358	66.5	190/345	55.1	11.4
Other	6/9	66.7	11/16	68.8	-2.1

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
Modified from Applicant's Table 11-21 of CSR, p 429

Statistical Reviewer's Comments:

In the Cefotetan group, the response rates by gender were higher in female and the response rates by race appear lower in Hispanics.

Overall, the results based on these subgroups were robust compared to the primary analysis results.

4.2 Other Special/Subgroup Populations

The proportion of patients with a favorable response in the EPP and MITT populations by bowel preparation are listed in Table 12, and Table 13 respectively.

Table 12 Analyses of Outcomes by Bowel Preparation (EPP Population)

	Ertapenem (A) (N=346)		**Cefotetan (B) (N=339)**		**Observed Differences (A-B)**
	Observed Response		**Observed Response**		
Bowel Preparation	n/m	%	n/m	%	%
Sodium Phosphate	131/184	71.2	122/191	63.9	7.3
Polyethylene Glycol	112/161	69.6	71/147	48.3	21.3

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
One ertapenem patient and one cefotetan patient were excluded from this analysis because they were missing bowel preparation type values.
Modified from Sponsor's Table 7-9 of CSR, p 126.

Table 13 Analyses of Outcomes by Bowel Preparation (MITT Population)

	Ertapenem (A) (N=451)		**Cefotetan (B) (N=450)**		**Observed Differences (A-B)**
	Observed response		**Observed Response**		
Bowel Preparation	n/m	%	n/m	%	%
Sodium Phosphate	165/245	67.4	154/257	59.9	7.4
Polyethylene Glycol	130/205	63.4	93/192	48.4	15.0

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
One ertapenem patient and one cefotetan patient were excluded from this analysis because they were missing bowel preparation type values.
Modified from Sponsor's Table 11-22 of CSR, p 430.

The proportion of patients with a favorable response in the EPP and MITT populations by Renal Function are listed in Table 14, and Table 15 respectively.

Table 14 Analyses of Outcomes by Renal Function (EPP Population)

	Ertapenem (A) (N=346)		Cefotetan (B) (N=339)		Observed Differences (A-B)
	Observed Response		Observed Response		
Creatinine Clearance Subgroup	n/m	%	n/m	%	%
$\leq$ 30 mL/min/1.73m^2	3/4	75.0	4/5	80.0	-5.0
> 30 mL/min/1.73m^2	236/329	71.7	185/324	57.0	14.7

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
13 ertapenem patients and 10 cefotetan patients were excluded from this analysis because they were missing creatinine clearance values.
Modified from Sponsor's table 7-10 of CSR, p 127.

Table 15 Analyses of Outcomes by Renal Function (MITT Population)

	Ertapenem (A) (N=451)		Cefotetan (B) (N=450)		Observed Differences (A-B)
	Observed Response		Observed Response		
Creatinine Clearance Subgroup	n/m	%	n/m	%	%
$\leq$ 30 mL/min/1.73m^2	4/5	80.0	5/8	62.5	17.5
> 30 mL/min/1.73m^2	285/428	66.6	235/428	54.9	11.7

N = Number of Evaluable patients in each treatment group.
n/m = Number of Evaluable patients with a favorable assessment / number of Evaluable patients with assessment.
CI = Confidence interval.
18 ertapenem patients and 14 cefotetan patients were excluded from this analysis because they were missing creatinine clearance values.
Modified from Sponsor's table 11-23 of CSR, p 431.

Statistical Reviewer's Comments:

Overall, the results based on these subgroups were robust compared to the primary analysis results.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Based on the 95% confidence interval (CI) for the clinical favorable response rates at 4-week post-treatment follow-up visit, the study demonstrated non-inferiority of Ertapenem Sodium 1g IV to the comparator (Cefotetan 2g IV) for the prophylaxis of surgical site infection following elective colorectal surgery in patients ≥ 18 years of age in both the EPP and MITT populations, using a 10% non-inferiority margin. The clinical favorable response rate of Ertapenem vs. Cefotetan in the EPP population was 70.6% vs. 57.3%, a 13.3% treatment difference (Table 5) with 95% confidence interval of (6.1%, 20.4%); and in the MITT population was 58.4% vs. 48.8%, a 9.6% treatment difference (Table 6) with 95% CI of (2.9%, 15.9%).

Sensitivity analyses in the overall population and the subgroup analyses were robust compared to the primary analysis results with respect to clinical favorable response at the 4-week post-treatment follow-up visit.

5.2 Conclusions and Recommendations

In conclusion, study 039 provided adequate evidence that Ertapenem Sodium 1g IV is non-inferior (within a 10% non-inferiority margin) to Cefotetan 2g IV for the prophylaxis of surgical site infection following elective colorectal surgery in patients ≥ 18 years of age.

SIGNATURES/DISTRIBUTION LIST

Yunfan Deng, Ph.D.
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/s/

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7/28/2006 03:06:18 PM
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Thamban Valappil
8/1/2006 01:39:23 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

Date Company Submitted: November 09, 2005
Date received by CDER: November 10, 2005
Date Assigned: March 06, 2006
Reviewer: Avery Goodwin, Ph.D.

NAME AND ADDRESS OF APPLICANT:

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P.O. Box 4, BLA-20
West Point PA
19486-0004

CONTACT PERSON:

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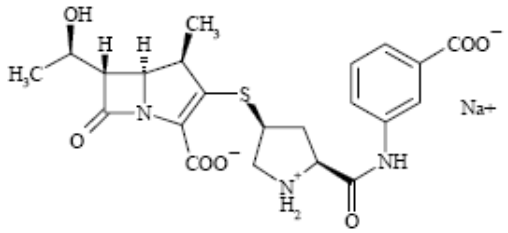
DRUG PRODUCT NAMES:

Proprietary Name: INVANZ
Established Name: Ertapenem
Structural Formula: $C_{22}H_{24}N_3O_7SNa$
Chemical Name: [4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt.



PROPOSED DOSAGE FORM AND STRENGTH:

Ertapenem sodium 1 g IV.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

IV will be given 60 minutes prior to the initial surgical incision as a single dose infused over 30 minutes

DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

INDICATION:

Colorectal Surgical Prophylaxis

RELATED SUBMISSION REVIEWED:

NDA 21-337

TYPE OF SUBMISSION:

This New Drug Application is submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act. Merck Research Laboratories submits the Application for the use of intravenous ertapenem sodium for prophylaxis prior to colorectal surgery.

PURPOSE OF SUBMISSION:

This NDA application is submitted in pursuant to Section 505(b) of the Food and Cosmetic Act.

EXECUTIVE SUMMARY:

Ertapenem is a long acting carbapenem antibiotic that was approved by the US Food and Drug Administration (FDA) in November 2001. It is approved for the treatment of several community-acquired and mixed aerobic/anaerobic infections, and moderate to severe complicated intra-abdominal infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* spp., *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron* or *Bacteroides uniformis*. Studies have also shown that ertapenem has a broad spectrum of activity against many bacteria associated with community-acquired infections, and those associated with complicated intra-abdominal infections.

Studies indicate that ertapenem has maintained its antimicrobial susceptibility profile against target pathogens. Ertapenem continues to demonstrate activity against methicillin-susceptible *S. aureus*, (b) (4) *Enterobacteriaceae*, *S. pneumoniae*, and *H. influenzae*. (b) (4)

The information describing the microbiology procedures, such as susceptibility testing methods, performed on isolates obtained during the prophylactic clinical trial of ertapenem is adequate. Methods established by the Clinical Laboratory Standards Institute (CLSI) (formerly NCCLS) were used.

The clinical evaluation by the Applicant showed that 72% of the patients in the evaluable population and 57.2% of the patients in the cefotetan group had a favorable clinical response assessment. The FDA Medical Officer's review showed that 70.6% of the patients in the evaluable population and 57.3% of the patients in the cefotetan group had a favorable clinical response assessment. Therefore, ertapenem is considered to be non-inferior to cefotetan for use as prophylaxis prior to colorectal surgery.

In the clinical Protocol 039, 124 pathogens were isolated from 30 patients in the ertapenem treatment group and 151 pathogens from 55 patents from the cefotetan treatment group. *Enterococcus, Enterococcus faecalis, and Staphylococcus aureus* were identified as the predominant isolates. In terms of Gram negative anaerobic organisms, *Bacteroides fragilis and Bacteroides thetaiotaomicron* were frequently observed. *Bacteroides fragilis* appeared evenly distributed across each treatment groups. However, *Bacteroides thetaiotaomicron* was seen most frequently in superficial incision infections in the cefotetan group. Gram negative aerobic bacilli were isolated in fewer numbers with *Escherichia coli* and *Pseudomonas aeruginosa* being the most frequently identified. The cefotetan treatment group had higher numbers of *Clostridium innocuum* and *Eubacterium lentum* and these isolates were commonly identified from superficial incision infections. Anaerobes were most frequently associated with superficial infection in the cefotetan treatment group while higher incidences of anaerobes were found in anastomotic leak. The significance of these findings is unknown.

The study demonstrated that isolates of enterococci from patients treated with ertapenem and cefotetan exhibited high levels of resistance to both drugs. *Staphylococcus aureus* isolated from patients in each group was also resistant to both study drugs. *Escherichia coli* identified in the study were susceptible to both study drugs. All species of *Bacteroides* identified were susceptible to ertapenem but showed varying levels of resistance to cefotetan. Additionally, *Clostridium innocuum* and *Eubacterium lentum* were generally susceptible to ertapenem but generally resistant to cefotetan. The majority of pathogens (66.7%) isolated and tested in the cefotetan group were resistant to cefotetan, whereas only 16.3% of the isolates tested in the ertapenem group were resistant to ertapenem.

MICROBIOLOGY SUBSECTION OF THE LABEL:

There are no suggested changes to the microbiology section of the label.

PACKAGE INSERT:

Microbiology
Ertapenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of

cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta-lactamases.
Ertapenem has been shown to be active against most isolates of the following microorganisms *in vitro* and in clinical infections. (See INDICATIONS AND USAGE):
Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus (methicillin susceptible isolates only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)
Streptococcus pyogenes
Note: Methicillin-resistant staphylococci and *Enterococcus* spp. are resistant to ertapenem.
Aerobic and facultative gram-negative microorganisms:
Escherichia coli
Haemophilus influenzae (Beta-lactamase negative isolates only)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis
Anaerobic microorganisms:
Bacteroides fragilis
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Clostridium clostridioforme
Eubacterium lentum
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella bivia
The following *in vitro* data are available, **but their clinical significance is unknown**.
At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem; however, the safety and effectiveness of ertapenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:
Aerobic and facultative gram-positive microorganisms:
Staphylococcus epidermidis (methicillin susceptible isolates only)
Streptococcus pneumoniae (penicillin-intermediate isolates only)
Aerobic and facultative gram-negative microorganisms:
Citrobacter freundii

Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae (Beta-lactamase positive isolates)
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic microorganisms:

Bacteroides vulgatus
Clostridium perfringens
Fusobacterium spp.

Susceptibility Test Methods:

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method[1,2] or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 4.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg ertapenem to test the susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria should be interpreted according to criteria provided in Table 4.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to ertapenem as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to criteria provided in Table 4.

Table 4
Susceptibility Interpretive Criteria for Ertapenem

Pathogen	Minimum Inhibitory Concentrations[a] MIC (μg/mL)			Disk Diffusion[a] Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae and *Staphylococcus* spp.	≤2.0	4.0	≥8.0	≥19	16-18	≤15
Haemophilus spp.	≤0.5	-	-	≥19	-	-
Streptococcus pneumoniae [b,c]	≤1.0	-	-	≥19	-	-
Streptococcus spp. other than *Streptococcus pneumoniae* [d,e]	≤1.0	-	-	≥19	-	-
Anaerobes	≤4.0	8.0	≥16.0	-	-	-

[a] The current absence of data in resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

[b] *Streptococcus pneumoniae* that are susceptible to penicillin (penicillin MIC ≤0.06 μg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[c] *Streptococcus pneumoniae* that are susceptible to penicillin (1-μg oxacillin disk zone diameter ≥20 mm), can be considered susceptible to ertapenem. Isolates with 1-μg oxacillin zone diameter ≤19 mm should be tested against ertapenem using an MIC method.

[d] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤0.12 μg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[e] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (10-units penicillin disk zone diameter ≥24 mm), can be considered susceptible to ertapenem. Isolates with 10-units penicillin disk zone diameter <24 mm should be tested against ertapenem using an MIC method. Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci and they should not be tested against ertapenem.

Note: *Staphylococcus* spp. can be considered susceptible to ertapenem if the penicillin MIC is ≤0.12 μg/mL. If the penicillin MIC is >0.12 μg/mL, then test oxacillin. *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin MIC is ≤2.0 μg/mL and resistant to ertapenem if the oxacillin MIC is ≥4.0 μg/mL. Coagulase

negative staphylococci can be considered susceptible to ertapenem if the oxacillin MIC is ≤0.25 µg/mL and resistant to ertapenem if the oxacillin MIC ≥0.5 µg/mL.

Staphylococcus spp. can be considered susceptible to ertapenem if the penicillin (10 U disk) zone is ≥29 mm. If the penicillin zone is ≤28 mm, then test oxacillin by disk diffusion (1µg disk). *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin (1µg disk) zone is ≥13 mm and resistant to ertapenem if the oxacillin zone is ≤10 mm. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin zone is ≥18 mm and resistant to ertapenem if the oxacillin (1µg disk) zone is ≤17 mm.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures[1,2,3,4]. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant. Standard ertapenem powder should provide the following range of values noted in Table 5.

Table 5
Acceptable Quality Control Ranges for Ertapenem

Microorganism	Minimum Inhibitory Concentrations MIC Range (µg/mL)	Disk Diffusion Zone Diameter (mm)
Escherichia coli ATCC 25922	0.004-0.016	29-36
Haemophilus influenzae ATCC 49766	0.016-0.06	27-33
Staphylococcus aureus	0.06-0.25	-

ATCC 29213		
Staphylococcus aureus ATCC 25923	-	24-31
Streptococcus pneumoniae ATCC 49619	0.03-0.25	28-35
Bacteroides fragilis ATCC 25285	0.06-0.5[f] 0.06-0.25[g]	-
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0[f] 0.25-1.0[g]	-
Eubacterium lentum ATCC 43055	0.5-4.0[f] 0.5-2.0[g]	-

[f] Quality control ranges for broth microdilution testing
[g] Quality control ranges for agar microdilution testing

REFERENCES

1. National Committee for Clinical Laboratory Standards (NCCLS) [Now Clinical and Laboratory Standards Institute (CLSI)]. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 7th Edition; Approved Standard, CLSI Document M7-A7. Clinical and Laboratory Standards Institute, Wayne, PA, January 2006.
2. Clinical and Laboratory Standards Institute (formerly NCCLS). Performance Standards for Antimicrobial Susceptibility Testing – 16th Informational Supplement. Approved Standard, Clinical and Laboratory Standards Institute (Formerly NCCLS) Document M100-S16. Clinical and Laboratory Standards Institute, Wayne, PA, January 2006.
3. National Committee for Clinical Laboratory Standards (NCCLS) [Now Clinical and Laboratory Standards Institute (CLSI)]. Performance Standards for Antimicrobial Disk Susceptibility Tests. 9th Edition; Approved Standard, CLSI Document M2-A9. Clinical and Laboratory Standards Institute, Wayne, PA, January 2006.
4. National Committee for Clinical Laboratory Standards (NCCLS) [Now Clinical and Laboratory Standards Institute (CLSI)]. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria* – Sixth Edition; Approved Standard, CLSI Document M11-A6. Clinical and Laboratory Standards Institute, Wayne, PA, January 2004.

DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

SUMMARY AND RECOMMENDATIONS

From the microbiology perspective, based on analysis of the information provided by the applicant, the Reviewer recommends approval of the prophylactic use of ertapenem for colorectal surgery.

INTRODUCTION AND BACKGROUND:

Carbapenems are β-lactam antibiotics with a carbon instead of sulfone in position 4 of the thyazolidinic moiety of the β-lactam ring[1]. It is generally accepted that carbapenems are stable to some clinically relevant β-lactamases, except for the Class B β-lactamases, also known as metalloenzymes. Studies have shown that Class B β-lactamases may be chromosomally encoded and can be found in *Stenotrophomonas maltophilia*, *Aeromonas* spp., *Bacillus cereus*, *Bacteroides fragilis*, *Flavobacterium* spp., and *Legionella gormanii*. Not all Class B β-lactamases are chromosomally encoded. Plasmid-borne metallo-β-lactamases have been found in *B. fragilis, P. aeruginosa, Acinetobacter baumannii* and certain *Enterobacteriaceae* such as *Serratia marcescens* and *Klebsiella pneumoniae*[1].

Ertapenem sodium is characterized as a long-acting, 1β-methyl parenteral Group 1 carbapenem with a broad spectrum of antimicrobial activity[2]. Ertapenem is a carbapenem antibacterial agent that has demonstrated activity against some aerobic and anaerobic Gram-positive and Gram-negative pathogens including *Streptococcus* species, methicillin-susceptible staphylococci, and the *Enterobacteriaceae*. In addition, ertapenem has in vitro activity against penicillin-resistant (penicillin minimum inhibitory concentration [MIC] ≥ 2 μg/mL) *Streptococcus pneumoniae* (PRSP) and against Gram-negative enterics carrying plasmid- or chromosomally-mediated β-lactamases, including the extended spectrum β-lactamase (ESBLs) and AmpC β-lactamases. Ertapenem has limited activity against hospital acquired pathogens such as methicillin-resistant staphylococci, and enterococci. Ertapenem shows very little activity against isolates of *Pseudomonas aeruginosa and Acinetobacter* spp. This is due to the presence of plasmid-borne metallo-β-lactamases[1].

Ertapenem was approved by the US Food and Drug Administration (FDA) in November 2001 for the treatment of several community-acquired and mixed aerobic/anaerobic infections, including moderate to severe complicated intra-abdominal infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* spp., *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron* or *Bacteroides uniformis*. Studies show that Ertapenem is resistant to a wide variety of β-lactamase enzymes, and has activity against many bacteria associated with community-acquired infections, and intra-abdominal infections. Ertapenem is also

approved for the following indications: 1) community-acquired pneumonia (CAP) 2) complicated urinary tract infection (cUTI) 3) complicated skin and skin structure infection (cSSSI), 4) intra-abdominal infection (IAI), and 5) acute pelvic infection (API). This supplement provides information on safety and efficacy to support the use of ertapenem for prophylaxis prior to colorectal surgery.

Activity *in vitro*:

The in vitro activity of ertapenem against a number of clinical isolates is summarized from published studies in the literature. The in vitro activity of ertapenem was compared with ceftriaxone, and piperacillin-tazobactam. Susceptibility testing with ertapenem, ceftriaxone, and piperacillin-tazobactam was primarily undertaken by broth microdilution, performed with pre-prepared antibiotic panels (b) (4) Methods established by the Clinical Laboratory Standards Institute (CLSI) (formerly NCCLS) were used [3, 4, 5]. The basal media used were those recommended by the CLSI, with cation-adjusted Mueller-Hinton broth used for nonfastidious organisms, cation-adjusted Mueller-Hinton broth supplemented with lysed horse blood used for streptococci, Haemophilus test medium used for fastidious gram-negative species, and Wilkins-Chalgren broth used for anaerobes.

Activity against various clinical isolates:

The MIC_{90}s of ertapenem, piperacillin-tazobactam and ceftriaxone against various clinical bacterial isolates from several large clinical studies published by Wexler [6] (2004) are summarized in Table 1-3. The summary attempts to show the current ertapenem resistance profile for anaerobes and aerobes based on the source of isolates.

Table 1. In vitro activity of ertapenem against Gram-positive bacteria

Strain	Source	MIC_{90} (mg/L)			Reference
		ertapenem	piperacillin–tazobactam	ceftriaxone	
Bacillus spp.	cancer, general	0.5–4	1	>32–>64	10, 11
Corynebacterium jeikeium	cancer, general	8–>32	8–32	1–32	7,10-13
Enterococcus faecalis	cancer, general, IAB	16–>64	4–8	>32–>64	7,8,10,12,14
Enterococcus faecium	cancer, general, IAB	>16–>64	>32	>32–>64	7,10,12,14
Enterococcus spp.	General, IAB, pelvic, SST	8–>16	4–128	>16–>32	7,9,13-16
*Enterococcus, vancomycin-*resistant	general	>32	>128	>32	11
*Enterococcus, vancomycin-*susceptible	general	>32	>128	>32	11
Listeria monocytogenes	cancer, general	0.15–0.5		>64	10,12
Micrococcus spp.	cancer	4		0.25	10
Rhodococcus spp.	cancer	2		2	10
S. aureus	general, SST	0.12–1	1–8	2–4	9,11,13
MRSA and *S. aureus, oxacillin-resistant*	general	16–>16	32		7,9,12
MSSA and S. aureus, oxacillin-susceptible	cancer, general, IAB, pelvic,	0.25–0.5	2–8	0.5–8	7-10,12,14-17
Staphylococcus epidermidis	general, SST	1–4	1	4	12,13
Staphylococcus haemolyticus	general	>16			12
Staphylococcus spp.	SST	0.25	1	2	13
Staphylococcus, coagulase-negative, methicillin-susceptible	cancer	2		8	10
Staphylococcus spp., coagulase- negative, oxacillin-susceptible	general	0.5			7
Staphylococcus spp., coagulase- negative	general	0.25–16	0.5–8	4–32	8,11
Staphylococcus spp., coagulase- negative, oxacillin-resistant	general	>16			37
Stomatococcus spp.	cancer	0.5		16	10
S. agalactiae	general, SST	0.06–0.125	0.5	0.125	7,9,11,16
Streptococcus Group C	general	0.25			12
Streptococcus Group G	cancer, general	<0.03		0.12	10,12
Streptococcus milleri group	SST	0.5	0.5	0.25	13
S. pneumoniae	general	0.25–2	2	0.5–1	8-10,17,18
penicillin-susceptible	general, pneumonia	<0.15–0.06	<0.06	0.03–0.06	7,9,11,17,19
penicillin-intermediate	general, pneumonia	0.5	2	0.5–1	7,9,11,17,19
penicillin-resistant	general, pneumonia	1–2	4	1–2	7,9,11,12,17,19,

quinolone-resistant, penicillin- susceptible	pneumonia	0.03		0.06	19
quinolone-resistant, penicillin- intermediate	pneumonia	1		1	19
quinolone-resistant	pneumonia	4		2	19
Streptococcus pyogenes	cancer, general, SST	<0.03–0.06	0.125–0.5	0.06–0.12	7-22,12,16
Streptococcus spp.	general	0.12–0.5	2	0.5	7,8
Streptococcus, viridans group	cancer, general	2–16	8	2–>64	10,11
Streptococcus, β-haemolytic	general, IAB, pelvic, SST	0.03–0.5	0.25–0.5	0.06–0.5	11,14-16

IAB, intra-abdominal infection; SST, skin and soft-tissue infection.

Table 2. In vitro activity of ertapenem against Gram-negative bacteria

Strain	Source	MIC_{90} (mg/L) ertapenem	MIC_{90} (mg/L) piperacillin–tazobactam	MIC_{90} (mg/L) ceftriaxone	Reference
A. baumannii	cancer, IAB	4–>16	128	32–64	10,14
Acinetobacter lwoffii	cancer	2		16	10
Acinetobacter spp.	general	8–16	256	128	7,8,12
Aeromonas spp.	general	0.25–4	256	0.5	7,8
Aeromonas hydrophila	cancer	1		64	10
Alcaligenes xylosoxidans	cancer	32		>64	10
Burkholderia cepacia	general	>16			7
Citrobacter spp.	IAB	<0.03–0.25	2–16	0.25–1	7,10,12,14
Citrobacter spp.	general	0.06	64	32	8
C. freundii	cancer	8		>64	10
E. aerogenes	cancer, general, IAB	0.25–1	8–256	2–128	8,10,12
Enterobacter agglomerans	cancer	<0.03		16	10
E. cloacae	cancer, general, IAB, pelvic, SST	0.06–1	4–256	0.25–32	8,10,12,14-16
Enterobacter spp.	general	0.25–0.5	16	32	7,9
Enterobacteriaceae, all	general, pneumonia	0.03–0.125	8	0.125–1	9,17
Enterobacteriaceae, other	general	0.06	4	1	9
E. coli	pelvic, cancer, general, IAB, SST	<0.016–0.12	2–128	0.06–0.25	7–12,14–16
E. coli, ESBL	general	0.5	>128	>32	11
H. influenzae	cancer, general, pneumonia	0.06–0.125	0.06–0.125	<0.008–0.5	8–11,17
β-lactamase-positive	pneumonia	0.06		<0.016	17
β-lactamase-negative	pneumonia	0.125		<0.016	17
H. parainfluenzae, β-lactamase-negative	pneumonia	0.125		0.03	17
Haemophilus spp.	general	0.06–0.25	1	0.25	7,8
Klebsiella, AmpC/wild type	general	0.12	>128	16	11
Klebsiella, ESBL producer		0.06			20

K. pneumoniae and Klebsiella spp.	pelvic, cancer, IAB, SST, general	<0.015–0.25	8–256	0.06–8	7–12,14–16
M. catarrhalis	general, pneumonia	0.016–<0.03		1	7,12,17
Moraxella spp.	general, SST	<0.015–0.008	<0.015–0.06	<0.015–0.25	8,13
M. morganii	cancer	8		>64	10
M. morganii	general	<0.03–0.06	32	8	8,12
Neisseria meningitidis	general	0.008–0.016	0.12	0.06	7,8
Neisseria spp.	SST	<0.015	<0.015	0.03	13
Pasteurella spp.	general, SST	<0.015–0.03	<0.015	<0.015	7,13
Proteeae	general	0.03			7
Proteus mirabilis	pelvic, cancer, general, IAB, SST	<0.016–0.06	0.5–32	<0.03–0.06	8,10,12,14-16
Proteus vulgaris	cancer, general, IAB	<0.03–0.25	1–2	0.25–128	8,10,12,14-16
Providencia rettgeri	general	4			12
Providencia spp.	general	0.25	16	8	8
P. aeruginosa	cancer, general, IAB, SST	16–>64	8–256	>32–>64	7–10,12,14,16
ceftazidime-resistant	general	>32	>128	>32	11
ceftazidime-susceptible	general	>32	32	>32	11
Pseudomonas spp.	cancer, general	>16–>64		>64	7,10
Salmonella spp.	general	<0.008–0.016	16	0.25	7,9
Serratia spp.	general	0.06–0.12	32	0.5–4	7,8,10,12
Shigella spp.	general	<0.008–0.015	64	0.06	7,8
Stenotrophomonas maltophilia	general, cancer	>16–>64		>64	7,10,12

IAB, intra-abdominal infection; SST, skin and soft-tissue infection.

Table 3. In vitro activity of ertapenem against anaerobic bacteria

Strain	Source	MIC_{90} (mg/L)			Reference
		ertapenem	piperacillin–tazobactam	ceftriaxone	
Anaerobes, all	general	0.5–1	16	128	8,9
B. fragilis group, indole-positive	SST	1	16		21
B. fragilis group	general, pelvic	1–4	4–32	>64–256	8,9,15,22
Bacteroides caccae	IAB	0.5–4	1–16	>128	23,24
B. distasonis	general, IAB	1–2	8–32	>64	23-26
B. fragilis	general, pelvic, IAB	1–2	1–4	64–>256	7,15,22-24,26
B. ovatus	general, IAB, general	1	4–16	>64–>128	23,24,26
Bacteroides capillosus and Bacteroides putredinis	pelvic	0.25	<0.06	32	15
Bacteroides stercoris/merdae	IAB	1	8	>128	23
Bacteroides thetaiotaomicron	general, IAB	1–2	4–32	>128	23–25
Bacteroides uniformis	general, IAB	1–2	2–16	>128	24–25

Bacteroides vulgatus	IAB, general	0.5–2	2–32		23–26
B. wadsworthia	general	0.062		2	34
B. wadsworthia	IAB	>32	>128	>128	23
Bacteroides ureolyticus/ Campylobacter	SST	>16	>16	>16	13
C. gracilis	general	0.12		>256	22
C. clostridioforme	IAB	4	128	64	23
C. difficile	general	8	16	64–>64	22,26
Clostridium innocuum	IAB	2	1	8	23
C. perfringens	general, IAB	0.06–0.0125	0.125–0.5	2–8	7,22,23,26
Clostridium ramosum	IAB	1	0.5	0.25	23
Clostridium spp.	general	1–2	1–2	4–16	8,15
Eubacterium lentum	IAB	1	32	1–>128	23
Eubacterium spp.	general, IAB, SST	0.25–1	0.125–16	1–>64	13,23,26
Fusobacterium spp.	IAB	0.03	<0.06	1	23
Fusobacterium mortiferum/varium	general	0.12–0.25	0.12–1	>64–256	22,24,26
Fusobacterium necrophorum	general	0.008	<0.125	<0.125	26
Fusobacterium nucleatum	general	0.062		2	22
Fusobacterium nucleatum	general	2		2	26
Fusobacterium spp.	pelvic	<0.015	0.05	0.05	15
Fusobacterium spp., animal isolates	SST	<0.015	<0.015	<0.015	13
Fusobacterium spp., human isolates	SST	0.03	<0.015	0.25	13
Fusobacterium varium	general	1	16	16	26
Lactobacillus spp.	IAB, general	>16–>32	4	>64–>128	23,26
NSF Gram-positive bacilli	IAB, pelvic, general, SST	0.5–1	1–2	0.25–8	13,15,22,23
Peptostreptococcus magnus	SST	0.5	0.25		21
P. micros	IAB, SST	0.06–0.25	<0.06–0.125	0.5	21,23
Peptostreptococcus spp.	general, IAB, pelvic, SST	0.2–1	0.25–2	4–16	12,15,22-24,26
Porphyromonas spp.	SST	<0.015–0.125	<0.015–1	0.03–4	13,15,21-24
Prevotella spp.	general	0.125–0.5	<0.06–1	2–64	13,15,21-24,26
Prevotella spp., pigmented	SST	0.125	<0.015	8	13
Propionibacterium spp.	general	0.12–0.25	1–2	0.5	7,8,26
Streptococcus, anaerobic	IAB	0.25	0.5	2	23
S. wadsworthensis	general	0.062		1	23
Veillonella spp.	SST	0.125	16	4	13

IAB, intra-abdominal infection; SST, skin and soft-tissue infection; NSF, non-spore forming.

To assess the in vitro activity of ertapenem isolates of bacterial pathogens were collected across centers in Europe and Australia[8]. The MIC_{90}s of ertapenem and comparators (piperacillin-tazobactam and ceftriaxone) were determined against 3500 isolates from 12 centers. Single centers were enrolled in Belgium, Denmark, France, Germany, Greece,

The Netherlands, Spain, Sweden, Switzerland, and the United Kingdom, together with two centers in Australia. Each center was asked to test unselected clinical isolates collected in 1999 and 2000 as follows: *Enterococcus faecalis* (*n* = 10), methicillin-susceptible *Staphylococcus aureus* (*n* = 20), coagulase-negative staphylococci (*n* = 20), *Streptococcus pyogenes* (*n* = 10), *Streptococcus pneumoniae* (*n* = 20), *Streptococcus* spp. (*n* = 10), *Citrobacter* spp. (*n* = 10), *Enterobacter aerogenes* (*n* = 10), *Enterobacter cloacae* (*n* = 10), *Escherichia coli* (*n* = 20), *Klebsiella oxytoca* (*n* = 10), *Klebsiella pneumoniae* (*n* = 20), *Morganella morganii* (*n* = 10), *Proteus mirabilis* (*n* = 20), *Proteus vulgaris* (*n* = 10), *Providencia rettgeri* (*n* = 10), *Providencia stuartii* (*n* = 10), *Salmonella* spp. (*n* = 10), *Serratia* spp. (*n* = 10), *Shigella* spp. (*n* = 10), *Aeromonas* spp. (*n* = 10), *Acinetobacter* spp. (*n* = 10), *P. aeruginosa* (*n* = 10), *Haemophilus influenzae* (*n* = 20), *Haemophilus* spp. (*n* = 10), *Moraxella* spp. (*n* = 10), *Neisseria meningitidis* (*n* = 10), and anaerobes (*n* = 20). Determination of the species of the isolates was by the laboratories' routine methods. Multiple isolates from a single patient were excluded. None of the centers enrolled were involved in clinical trials with ertapenem.

Ertapenem was the most active agent tested against isolates of the family *Enterobacteriaceae*, with MICs at which 90% of isolates are inhibited (MIC_{90}s) of 1 μg/ml or less for all species were reported. Ceftriaxone and piperacillin-tazobactam had low MIC_{50}s for isolates of the *Enterobacteriaceae*, but MIC_{90}s were raised for many species and groups.

In another large survey of 5558 isolates from 11 North American centers, MIC_{90}s of ertapenem for all species of Enterobacteriaceae were reported to range from ≤ 0.008 mg/L for *Salmonella* and *Shigella* spp. to 0.5 mg/L for *Enterobacter* spp. Oxacillin-resistant staphylococci and enterococci were resistant to ertapenem, and *Acinetobacter* and *Pseudomonas* species were resistant to ertapenem[7].

In a study by Jones (2001)[11], isolates without known resistant mechanisms were tested for their sensitivity against ertapenem. The study found that ertapenem MIC_{90}s for isolates of *E. coli* and *Klebsiella* without known resistance mechanisms were ≤ 0.015 mg/L. MIC_{90}s for *Haemophilus*, β-haemolytic *Streptococcus*, viridans group streptococci and *S. aureus* were 0.06, 0.03, 2 and 0.12 mg/L, respectively. MIC_{90}s for pneumococci varied with susceptibility to penicillin (0.015, 0.5 and 2 mg/L for susceptible, intermediate and resistant, respectively).

The *in vitro* activity of ertapenem against 381 respiratory bacterial pathogens isolated from patients with community-acquired pneumonia and exacerbation of chronic bronchitis was determined[17]. Ertapenem MIC_{90}s for the some of the isolates tested were as follows: *Enterobacteriaceae*, 0.125 mg/L; β-lactamase-positive *H. influenzae,* 0.06 mg/L; β-lactamase-negative *H. influenzae.* 0.125 mg/L; *Haemophilus parainfluenzae,* 0.125 mg/L; *M. catarrhalis* 0.016 mg/L; and methicillin sensitive *S. aureus* (MSSA),

0.25 mg/L. There were nine resistant MRSA and one of 11 penicillin-resistant *S. pneumoniae* isolate. For all the other isolates, the MIC90s were ≤ 0.25 mg/L, except for the presence of 13 penicillin-intermediate *S. pneumoniae* isolates, for which the MIC_{90}s were 0.5 mg/L.

In another study, the activity of ertapenem against 102 clinical isolates of S. *pneumoniae*[18] was investigated. MIC_{90}s of ertapenem, imipenem and meropenem were 2, 0.5 and 1 mg/L, respectively. Ertapenem MIC_{90}s increased according to penicillin susceptibility (0.03, 0.5 and 2 mg/L for penicillin-susceptible, -intermediate and -resistant strains, respectively), the 33 penicillin-intermediate isolates were inhibited by ertapenem at ≤ 1 mg/L and 68% of fully penicillin-resistant organisms were inhibited at this concentration. In general, pneumococci that were resistant to β-lactams or carbapenems also had higher resistance rates to ertapenem.

Skin and soft tissue infections:

Goldstein *et al.*[21] studied the effect of ertapenem against organisms associated with complicated skin and skin-structure infections. The primary pathogens are *S. aureus* and β-haemolytic streptococci; although a number of Gram-positive and Gram-negative aerobic and anaerobic bacteria may be involved. In that study, 232 anaerobes including Gram-negative species (*Bacteroides, Prevotella*, *Porphyromonas*, *Fusobacterium*, *Biophilia*, *Dialister pneumosintes* and *Veillonella* species), Gram-positive cocci and other Gram-positive bacilli were isolated from patients. MIC_{90}s for the organisms tested are summarized in Tables 1–3. Briefly, 137 of 141 anaerobes tested (97.2%) were susceptible to ertapenem. Four *Peptostreptococcus* isolates were either intermediate or resistant to ertapenem.

In another study[16], 518 aerobic and facultative bacterial pathogens were also tested for susceptibility to ertapenem. The ertapenem MIC was ≤ 2 mg/L for 80.9% of the isolates and ≥ 8 mg/L for 16.2% of the isolates. MIC_{90}s for the major groups isolated were: MSSA 0.25 mg/L, *S. pyogenes* 0.03 mg/L and *E. coli* ≤ 0.016 mg/L. Resistant isolates included enterococci, MRSA, *P. aeruginosa* and other non-fermentative Gram-negative bacilli.

Ertapenem was active against pathogens associated with bite-wound infections[13]. Ertapenem was only moderately active against *Corynebacterium* spp. (MIC_{90} 4 mg/L), *Staphylococcus epidermidis* (MIC_{90} 4 mg/L) and *Enterococcus* species (MIC_{90} 8 mg/L). *Eubacterium* species isolated from these infections were more susceptible to ertapenem and to piperacillin–tazobactam than those isolated from other types of infection. *Campylobacter* species were the most resistant: five strains of *Campylobacter* (four of five strains of *Campylobacter gracilis* and one of three strains of *Campylobacter rectus*) required ertapenem ≥ 16 mg/L for inhibition.

Activity against intra-abdominal anaerobic infections:

Intra-abdominal infection includes a wide variety of markedly different conditions, ranging from primary and secondary peritonitis to intra-hepatic infection to diverticulitis, appendicitis, and intra-abdominal abscess. The choice of antimicrobial therapy must take into account the complex density of bacteria normal aerobic and anaerobic flora of the bowel. The intestinal colonic flora contains 10^{12} bacteria/gm of feces, which are predominantly anaerobic, and anaerobic species outnumber aerobes by 1000 to 1[27]. *Bacteroides fragilis* is reported to account for only 0.5% of the normal colonic flora; however, it is recognized as the single most important anaerobic pathogen.

Goldstein *et al*. (2000) [23] studied ertapenem's *in vitro* activity against 1001 anaerobes isolated from intra-abdominal infections from 29 sites in 17 countries worldwide. Ertapenem was active against all isolates, including all members of the *B. fragilis* group species (MIC_{90}s were 1 or 2 mg/L), with the exception of 20% of *Biophilia wadsworthia* isolates, 3 isolates of lactobacilli, and 1 isolate of *Acidaminococcus fermentans*. MIC_{90}s were species specific for *Clostridium*, ranging from 0.06 mg/L for *Clostridium perfringens* to 4 mg/L for *Clostridium clostridioforme*. *Porphyromonas*, *Peptostreptococcus* and *Fusobacterium* species were very susceptible to ertapenem. The most resistant organisms were *Lactobacillus* spp. and *Biophilia wadsworthia* (MIC_{90} > 32 mg/L). No differences were noted in the overall geographical susceptibilities of the anaerobes to ertapenem.

In another study, the in vitro activity of ertapenem against 244 isolates of anaerobic bacterial found in intra-abdominal infections was investigated by Vu *et al*. (2002)[29]. Ertapenem MIC_{90}s were 4 mg/L for *B. fragilis* and *Bacteroides ovatus* and ≤ 2 mg/L for the other *B. fragilis* group species. A few isolates of *Clostridium difficile* had ertapenem MICs of 8 mg/L and six isolates of *Clostridium innocuum* had MICs of 4 mg/L. The isolates of *Lactobacillus* and *Biophilia* were not as resistant as those studied by Goldstein *et al*[23]. The ertapenem MIC_{90} for *B. wadsworthia* was 0.25 mg/L; MICs for one strain of *Lactobacillus jensenii* and one strain of *Sutterella wadsworthensis* were 4 mg/L. The authors of the study stated that *Biophilia* MICs can be very difficult to read, especially with carbapenems, and it is possible that the differences noted here are technical and not reflections of real differences in resistance rates.

Conclusion:

The data indicate that ertapenem has antimicrobial activity against the Gram-positive and Gram-negative bacteria, including *Enterobacteriaceae*, *Streptococcus pneumoniae* and some species of anaerobic bacteria. Isolates from a variety of infections such as those associated with community-acquired pneumonia are inhibited by ertapenem. Ertapenem

is active against aerobic, facultative and anaerobic pathogens found in complicated skin and soft tissue infections. The activity of ertapenem appears similar to piperacillin-tazobactam in activity against anaerobic isolates isolated from these infections. Ertapenem also demonstrated activity against isolates found in bite wounds except for those described above. Ertapenem was not active against the *Campylobacter* isolates tested.

The data also show that ertapenem is active against anaerobic isolates associated with intra-abdominal infections and against some anaerobes except for organisms that are known to be resistant to ertapenem (i.e. enterococci, MRSA, *Acinetobacter* and *P. aeruginosa*). In another published findings on the survey of *Bacteroides* susceptibility to antimicrobial agents, metronidazole, imipenem, meropenem, ertapenem, ampicillin–sulbactam, piperacillin–tazobactam and ticarcillin–clavulanate have maintained excellent activity[30]. Increased resistance to the quinolones, including trovafloxacin and clinafloxacin, has been noted. The newest quinolone, moxifloxacin, has shown resistance rates strikingly similar to those of trovafloxacin for *Bacteroides* species[31]. Although imipenem metallo-β-lactamase, which can confer resistance to all current carbapenems, has been reported in Japan, its presence in the USA and Europe appear to be limited. In addition, although Metronidazole resistance genes have been reported in Europe, they have not been common in the USA, and metronidazole resistance has been very rare in *Bacteroides*.

The Surgical Infection Society supports the use of monotherapy for intra-abdominal infections. Agents such as ertapenem, listed under monotherapy, have good antimicrobial activity against intra-abdominal pathogens. It is reported that resistance to cefoxitin or cefotetan may be significant for some species of *Bacteriodies*[32].

Mechanism of Action:

The mechanism of action of ertapenem has been previously reviewed (NDA 21-337). Briefly, the bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin-binding proteins (PBPs). Ertapenem binds most strongly to penicillin binding protein (PBP)-2 of *Escherichia coli*, then PBP-3, and has good affinity for PBP-1a and -1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases and cephalosporinases and extended spectrum beta-lactamases.

PK DATA FOR ERTAPENEM:

Ertapenem sodium has an extended half-life of ~4 hours allowing for once daily dosing in therapeutic regimens. After a single 1-g dose of ertapenem intravenously, a Cmax of 155

µg/mL is reached, and the plasma concentration of total drug is 31 µg/mL at 6 hours and 9 µg/mL at 12 hours dose. The plasma concentration of total drug declines to 3 µg/mL at 18 hours.

Ertapenem penetration into interstitial fluid has been studied using the suction skin blister model. These data, which were included with the original ertapenem application, indicate penetration of ertapenem into blister fluid after 1-g IV once daily dosing. Peak skin blister concentrations of 24 µg/mL are achieved at 4 to 8 hours after dosing and sustained above 4 µg/mL for the entire dosing interval. The sponsor states that the concentration of ertapenem in skin blister fluid should exceed 4 µg/mL within 1 hour of dosing. The sponsor has indicated that this level is well above the MIC_{90} of the anticipated pathogens in surgical infections following colorectal surgery (e.g., *S. aureus*, Gram-negative enterics and anaerobes), all with $MIC_{90} \leq 1.0$ µg/mL. It is also stated that while the dose would be administered 1 hour prior to the surgical incision, repeat dosing would not be required even if there were substantial delay to the initiation of surgery, or with prolonged procedure.

Cefotetan is a second generation cephalosporin with anti-anaerobic activity and an extended half life of approximately 4 hours. It has been studied extensively and shown to be effective and is approved worldwide as a single dose for use in the prophylaxis of clean-contaminated surgery, including colorectal surgery. Studies have shown that a single 2 gram dose of cefotetan administered within 1 hour prior to surgery is effective in colorectal and other clean-contaminated surgeries at reducing the incidence of subsequent surgical site infection.

CLINICAL STUDIES (PROTOCOL 039):

SUSCEPTIBILITY TEST METHODS AND METHODS FOR DETECTION OF RESISTANCE:

Microbiologic Cultures:

All patient specimens from postoperative infections were appropriately obtained from the site of infection and for culture. At the time of specimen collection, 2 specimens from each site of infection were to be prepared. Aerobic cultures were to be performed according to local procedures by the local laboratory. Anaerobic culture of specimens was done at the central lab (b) (4) The sponsor did not submit the details of specimen collection; specimen transport; and specimen processing.

In Vitro Antibiotic Susceptibilities of Etiologic Pathogens:

All organisms considered to be pathogens were tested for in vitro susceptibility to ertapenem and cefotetan in the investigator's laboratory using the disk diffusion method as outlined in

the Clinical Laboratory Standards Institute (CLSI) - formerly NCCLS documents M2-A5, and M2-A6. Disk diffusion susceptibility testing using antimicrobial agents other than the study antibiotics were carried out (i.e., identification of MRSA or PRSP), according to the standard testing methodology used by the investigator's microbiology laboratory. Established disk interpretive standards were used for determination of susceptibilities to antimicrobial agents other than the study antibiotics. The sponsor states that although all organisms considered by the investigator to be pathogens were to be primarily tested for in vitro susceptibility using the disk diffusion method, standardized agar or broth dilution tests could have been performed at the discretion of the investigator's microbiology laboratory. The type of dilution test system used was recorded on the appropriate case report form. Based on the data provided by the applicant, both disk diffusion and broth micro dilution were used.

Interpretive standards established by the FDA were used for determining the susceptibilities to ertapenem and cefotetan. All in vitro susceptibility testing was performed by a central laboratory (as previously noted). Interpretive standards for the determination of susceptibility to ertapenem per FDA are shown on Table 4.

Table 4: FDA approved ertapenem MIC interpretive criteria/disk diffusion zone diameter interpretive criteria

Pathogen	**Ertapenem**					
	Dilution MIC (µg/mL)			**Disk Diffusion Zone of Diameters (mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2	4	≥8	≥19	16 – 18	≤15
Staphylococcus spp. (methicillin-susceptible only)	≤2	4	≥8	≥19	16 – 18	≤15
Haemophilus spp	≤0.5	-	-	≥19	-	-
S. pneumoniae (Penicillin – susceptible) Non-meningitis Meningitis	 ≤1 NA	 -	 -	-	-	-
Streptococcus spp (other than *S. pneumoniae)* *Beta-hemolytic group* *Viridans group*	≤1	-	-	≥19	-	-
Anaerobes	≤4	8	≥16	-	-	-

S= susceptible; I= intermediate; R=resistant

Clinical Microbiology:

Protocol 039 was a multicenter, double-blind, randomized study designed to evaluate the safety, efficacy and tolerability of ertapenem versus cefotetan for prophylaxis of primary surgical site infection following elective colorectal surgery in patients' ≥ 18 years of age. The rationale for investigating ertapenem in this indication is based on the appropriate

aerobic and anaerobic spectrum of activity of ertapenem, its proven efficacy in the treatment of mixed aerobic/anaerobic intra-abdominal and pelvic infections and its extended half-life of making it potentially suitable as a single dose perioperative prophylactic agent. The study was designed to show non-inferiority of the ertapenem sodium group to the comparator (cefotetan) group.

For the primary analysis, 338 out of 476 treated patients (71.0%) in the ertapenem group and 334 out of 476 treated patients (70.2%) in the cefotetan group were evaluable. The sponsor states that patients were stratified for balance across the treatment groups at study entry by surgical procedure. Excluded from the study were patients who required emergent surgery or those with infection at the time of surgery. Also excluded, were those who had received systemic antibacterial therapy within the week preceding surgery. Adult patients scheduled to undergo elective colon or colorectal surgery by laparotomy (surgical incision into the abdominal wall) with sufficient time for mechanical bowel preparation were randomized to 1 of the 2 study regimens in a 1:1 ratio. Patients were stratified by planned surgical procedure; stratum I being those patients with a planned intraperitoneal procedure, and stratum II being those patients planned to have an abdominoperineal resection. Patients were to receive a single prophylactic dose of either ertapenem (1 g) or cefotetan (2 g) within 60 minutes prior to the planned initial surgical incision and were followed for 4-weeks postoperatively for failure of prophylaxis.

Clinical response assessments were made by the investigator at hospital discharge and at the follow-up visit 4 weeks post treatment. Three potential clinical responses as defined in the protocol were 1) success of prophylaxis, 2) failure of prophylaxis, and 3) distant site infection. Success of prophylaxis required that each of the three following criteria had been met:

- No signs or symptoms of infection at the surgical site.
- No further antimicrobial therapy was necessary.
- No surgical intervention for infection was necessary.

Failure of prophylaxis was the final clinical outcome if one of the following had occurred:

- Development of either a superficial, deep incision or intra-abdominal organ/space surgical site infection in the primary operative incision(s) within 30 days after the Operation
- Any unexplained use of antibiotics within the 4 weeks following colorectal surgery
- Anastomotic leak of the involved bowel requiring additional intervention by surgery or use of antimicrobials within 30 days after the operation.

Distant site infection was recorded as an outcome when a patient received systemic antimicrobial therapy for a documented infection considered unrelated to the original

surgical site (e.g. urinary tract infection, pneumonia, vascular catheter-related infection or other).

Patient Populations:

Two approaches, evaluable per-protocol (EPP) and modified-intention-to-treat (MITT) were applied to the analysis of efficacy in Protocol 039. EPP was considered primary in the study since this population is potentially less confounded by events unrelated to surgical site infection and/or the efficacy of prophylaxis. The EPP and MITT populations were determined by Merck clinical research personnel prior to unblinding the study and were based on pre-specified criteria as described in the Efficacy Evaluability Criteria document in the Prospective Data Analysis Plan (DAP) for the study. The MITT analyses were carried out secondarily to corroborate results from the primary EPP analyses. The 2 treatment groups were similar with respect to baseline characteristics and the EPP population was similar to the MITT and randomized populations. The following is a description of the study EPP and MITT populations included in the efficacy analyses:

MITT Population: all patients randomized and treated, who had elective open surgery of the colon or rectum with completion of mechanical bowel preparation procedure and who received a complete dose of study medication at any time before or during surgery.

EPP Population: a subset of the MITT population comprised of patients who received a complete dose of prophylaxis no more than two hours prior to initial surgical incision and no more than six hours before surgical closure, who have had primary skin closure, and in whom sufficient information was available to determine the outcome of prophylaxis at the 4-week follow-up assessment with no confounding factors present that interfered with that assessment (e.g. other systemic antibiotics or other prophylactic use of an antiinfective agent not allowed by protocol such as antibiotic in lavage fluid).

Efficacy Endpoints:

All planned analyses were defined prospectively in the DAP for the study. The primary objective of the study was to compare, in the EPP population, the effectiveness of single-dose ertapenem and cefotetan as prophylaxis for elective colorectal surgery. The primary assessment was the proportion of patients determined to have had successful surgical prophylaxis at the 4- week posttreatment follow-up evaluation. Patients experiencing both a failure of prophylaxis and a distant site infection were considered to be an evaluable failure of prophylaxis for the primary endpoint. Otherwise patients who received confounding antibacterial therapy for a distant-site infection were excluded from the primary EPP analysis

According to the sponsor, the major reasons for exclusion from the EPP population in both groups were 1) distant site infection with concomitant antibiotic administration and no evidence of subsequent surgical wound infection, 2) prior or concomitant antibiotic violation or 3) having received study prophylaxis outside of the Protocol defined perioperative window (within 2 hours prior to surgery or greater than 6 hours before skin

closure). Patients with these exclusions for the EPP population were generally included in the MITT analyses.

Clinical Efficacy Results:

The primary efficacy analysis was performed on the clinically EPP population and assessed the overall success of antibacterial prophylaxis 4 weeks post-treatment. The analysis results by the Applicant and FDA Medical Officer are shown in Table 5. All patients who were not considered previous failures were excluded from the analysis if they were missing a follow-up assessment. Additionally, patients who received concomitant antibacterial therapy for a distant site infection without evidence of surgical site infection were also excluded from this analysis because the additional antibacterial therapy was considered to have possible confounded the outcome assessment; patients with distant site infection were considered prophylaxis failures if they also had evidence of surgical site infection. The Applicant's assessment showed that 72% of the patients in the evaluable population and 57.2% of the patients in the cefotetan group had a favorable clinical response assessment. The FDA assessment showed that 70.6% of the patients in the evaluable population and 57.3% of the patients in the cefotetan group had a favorable clinical response assessment. In the MITT population, 58.4% of the patients in the ertapenem and 48.8% in the cefotetan group had a favorable clinical response assessment. Taken together, these results indicate that ertapenem (1 gram) administered as a single IV dose 1 hour prior to surgery is non-inferior to cefotetan (2 gram) for prophylaxis of elective colorectal surgery. Moreover, ertapenem appear more effective than cefotetan with respect to the success of surgical prophylaxis at the 4 week follow-up assessment.

Table 5: Clinical Response (Evaluable and MITT populations)

	Ertapenem (A)				**Cefotetan (B)**					
	Estimated[¥] Response				**Estimated[¥] Response**				**Estimated[¥] Difference (A - B)**	
Analysis Set	N	n	%	(95% CI)	N	n	%	(95% CI)	%	(95% CI)
Evaluable										
Applicant	338	243	72.0	(67.2, 76.8)	334	191	57.2	(51.9, 62.6)	14.8	(7.5, 21.9)
Medical Officer	346	244	70.6	(65.8, 75.4)	339	194	57.3	(52.0, 62.6)	13.3	(6.1, 20.4)
MITT										
Applicant	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)
Medical Officer	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)

[¥] Computed from a statistical model adjusting for surgical procedure.

N = Number of Evaluable patients in each treatment group.

n = Number of Evaluable patients with a favorable clinical response each treatment group.

CI = Confidence interval.

Applicant's results for Evaluable and MITT from Tables 7-1 (p. 99) of the CSR and the 4/27/06 Information Amendment, respectively.

Microbiology of Failures:

The applicant states that if a patient developed a postoperative infection at the surgical site or in circumstances of an anastomotic leak, specimens from the surgical site were to be appropriately obtained and sent for aerobic and anaerobic culture. The number (%) of documented pathogens from the surgical site is summarized by treatment group for the evaluable population in Table 6.

Table 6: Documented Pathogens Surgical Source† (Evaluable Population).

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	Ertapenem	Cefotetan
	(N=338)	(N=334)
	n=30	n=55
	m (%)	m (%)
All Documented Pathogens	124	151
gram-positive aerobic cocci	42 (33.9)	51 (33.8)
Abiotrophia	1 (0.8)	0 (0.0)
Enterococcus	8 (6.5)	11 (7.3)
Enterococcus avium	1 (0.8)	1 (0.7)
Enterococcus durans	1 (0.8)	0 (0.0)
Enterococcus faecalis	4 (3.2)	10 (6.6)
Enterococcus faecium	1 (0.8)	3 (2.0)
Enterococcus gallinarum	0 (0.0)	1 (0.7)
Enterococcus raffinosus	1 (0.8)	0 (0.0)
Enterococcus sp.	0 (0.0)	1 (0.7)
Staphylococcus	4 (3.2)	3 (2.0)
Staphylococcus aureus	9 (7.3)	10 (6.6)
Staphylococcus aureus MRSA	2 (1.6)	2 (1.3)
Staphylococcus aureus MSSA	4 (3.2)	3 (2.0)
Staphylococcus aureus Non Spec	3 (2.4)	5 (3.3)
Staphylococcus epidermidis	1 (0.8)	1 (0.7)
Staphylococcus sciuri	1 (0.8)	0 (0.0)
Streptococcus	4 (3.2)	3 (2.0)
Streptococcus agalactiae	1 (0.8)	4 (2.6)
Streptococcus milleri	2 (1.6)	0 (0.0)
Streptococcus viridans	3 (2.4)	3 (2.0)
gram-positive aerobic bacilli	3 (2.4)	0 (0.0)
Bacillus	2 (1.6)	0 (0.0)
Corynebacterium	1 (0.8)	0 (0.0)
gram-negative aerobic bacilli	17 (13.7)	23 (15.2)
Acinetobacter baumannii	1 (0.8)	0 (0.0)
Aeromonas hydrophila	0 (0.0)	1 (0.7)
Enterobacter aerogenes	0 (0.0)	2 (1.3)
Enterobacter cloacae	1 (0.8)	1 (0.7)
Escherichia coli	7 (5.6)	7 (4.6)
Klebsiella pneumoniae	1 (0.8)	2 (1.3)
Morganella morganii	0 (0.0)	2 (1.3)
Proteus mirabilis	3 (2.4)	1 (0.7)
Pseudomonas	1 (0.8)	0 (0.0)
Pseudomonas aeruginosa	3 (2.4)	7 (4.6)

Table 6: continued

	Ertapenem	Cefotetan
	(N=338)	(N=334)
	n=30	n=55
	m (%)	m (%)
gram-positive anaerobic cocci	5 (4.0)	4 (2.6)
Anaerococcus prevotii	1 (0.8)	0 (0.0)
Peptostreptococcus anaerobius	0 (0.0)	2 (1.3)
Peptostreptococcus magnus	2 (1.6)	1 (0.7)
Peptostreptococcus micros	2 (1.6)	0 (0.0)
Ruminococcus hansenii	0 (0.0)	1 (0.7)
gram-positive anaerobic bacilli	20 (16.1)	26 (17.2)
Bifidobacterium catenulatum	1 (0.8)	0 (0.0)
Clostridium	1 (0.8)	1 (0.7)
Clostridium clostridiiforme	0 (0.0)	1 (0.7)
Clostridium difficile	1 (0.8)	0 (0.0)
Clostridium hastiforme	1 (0.8)	0 (0.0)
Clostridium innocuum	2 (1.6)	8 (5.3)
Clostridium nexile	1 (0.8)	0 (0.0)
Clostridium perfringens	1 (0.8)	0 (0.0)
Clostridium ramosum	2 (1.6)	1 (0.7)
Eubacterium	3 (2.4)	2 (1.3)
Eubacterium biforme	0 (0.0)	1 (0.7)
Eubacterium lentum	3 (2.4)	8 (5.3)
Eubacterium limosum	0 (0.0)	1 (0.7)
Eubacterium tortuosum	0 (0.0)	1 (0.7)
Lactobacillus plantarum	3 (2.4)	0 (0.0)
Propionibacterium acnes	0 (0.0)	2 (1.3)
gram-positive anaerobic bacillus	1 (0.8)	0 (0.0)
gram-negative anaerobic cocci	0 (0.0)	2 (1.3)
Acidaminococcus fermentans	0 (0.0)	1 (0.7)
Veillonella	0 (0.0)	1 (0.7)
gram-negative anaerobic bacilli	7 (5.6)	2 (1.3)
Desulfovibrio fairfieldensis	0 (0.0)	1 (0.7)
Porphyromonas asaccharolytica	3 (2.4)	0 (0.0)
Porphyromonas cangingivalis	1 (0.8)	0 (0.0)
Prevotella intermedia	0 (0.0)	1 (0.7)
Sutterella wadsworthensis	1 (0.8)	0 (0.0)
gram-negative anaerobic bacillus	2 (1.6)	0 (0.0)

Table 6: continued

	Ertapenem	Cefotetan
	(N=338)	(N=334)
	n=30	n=55
	m (%)	m (%)
gram-negative anaerobic coccobacilli	29 (23.4)	40 (26.5)
Bacteroides caccae	1 (0.8)	0 (0.0)
Bacteroides capillosus	1 (0.8)	0 (0.0)
Bacteroides distasonis	1 (0.8)	4 (2.6)
Bacteroides fragilis	9 (7.3)	12 (7.9)
Bacteroides merdae	1 (0.8)	1 (0.7)
Bacteroides ovatus	3 (2.4)	3 (2.0)
Bacteroides sp.	0 (0.0)	1 (0.7)
Bacteroides stercoris	1 (0.8)	2 (1.3)
Bacteroides thetaiotaomicron	5 (4.0)	10 (6.6)
Bacteroides uniformis	2 (1.6)	2 (1.3)
Bacteroides vulgatus	4 (3.2)	3 (2.0)
Fusobacterium mortiferum	0 (0.0)	1 (0.7)
Fusobacterium russii	0 (0.0)	1 (0.7)
Fusobacterium varium	1 (0.8)	0 (0.0)
gram-negative bacilli	1 (0.8)	2 (1.3)
gram-negative bacillus	1 (0.8)	2 (1.3)
bacterial organisms	0 (0.0)	1 (0.7)
Bacteria	0 (0.0)	1 (0.7)

[1] Isolates obtained from surgical site infection or anastomotic leak failures.

The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.

N = Number of evaluable patients in each treatment group.

n = Number of patients with a documented pathogen in each treatment group.

m = Number of documented pathogens.

% = Number of documented pathogens / all pathogens.

One hundred and twenty four (124) pathogens were isolated from 30 patients in the ertapenem group and 151 pathogens were isolated from 55 patients in the cefotetan group. The most frequently isolated pathogens were gram positive aerobic cocci with *Enterococcus spp., Enterococcus faecalis, and Staphylococcus aureus* being the predominate organisms identified. Gram negative anaerobic coccobacilli were also isolated with *Bacteroides fragilis and Bacteroides thetaiotaomicron* being the most frequently isolated. Gram negative aerobic bacilli were isolated in fewer numbers with *Escherichia coli* and *Pseudomonas aeruginosa* being the most frequently identified. Gram positive anaerobic bacilli were isolated but no organisms were frequently seen with the exception of *Clostridium innocuum* and *Eubacterium lentum* in the cefotetan group. In general, the pathogens identified were similar across the treatment groups in both class and specific pathogen isolated with the exception of the *Clostridium innocuum* and *Eubacterium lentum* isolated in the cefotetan group. The number (%) of documented pathogens from the surgical site displayed by type of surgical site infection is summarized by

treatment group for the evaluable population in Table 7.

Table 7: Documented Pathogens – Surgical Source† Displayed by Type of Surgical Site Infection or Anastomotic Leak (Evaluable Population)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
All Documented Pathogens	11		19		21		27		43		71		49		34	
gram-positive aerobic cocci	3	(27.3)	7	(36.8)	4	(19.0)	13	(48.1)	22	(51.2)	20	(28.2)	13	(26.5)	11	(32.4)
Abiotrophia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Enterococcus	0	(0.0)	3	(15.8)	1	(4.8)	4	(14.8)	4	(9.3)	3	(4.2)	3	(6.1)	1	(2.9)
Enterococcus avium	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus durans	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus faecalis	1	(9.1)	1	(5.3)	0	(0.0)	0	(0.0)	2	(4.7)	4	(5.6)	1	(2.0)	5	(14.7)
Enterococcus faecium	0	(0.0)	1	(5.3)	0	(0.0)	1	(3.7)	1	(2.3)	0	(0.0)	0	(0.0)	1	(2.9)
Enterococcus gallinarum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Enterococcus raffinosus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Enterococcus sp.	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcus	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	2	(2.8)	2	(4.1)	1	(2.9)
Staphylococcus aureus	1	(9.1)	1	(5.3)	1	(4.8)	1	(3.7)	7	(16.3)	6	(8.5)	0	(0.0)	2	(5.9)
Staphylococcus aureus MRSA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.7)	1	(1.4)	0	(0.0)	1	(2.9)
Staphylococcus aureus MSSA	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	3	(7.0)	2	(2.8)	0	(0.0)	1	(2.9)
Staphylococcus aureus Non Spec	0	(0.0)	1	(5.3)	1	(4.8)	1	(3.7)	2	(4.7)	3	(4.2)	0	(0.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Staphylococcus epidermidis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	1	(1.4)	0	(0.0)	0	(0.0)
Staphylococcus sciuri	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Streptococcus	0	(0.0)	0	(0.0)	1	(4.8)	3	(11.1)	2	(4.7)	0	(0.0)	1	(2.0)	0	(0.0)
Streptococcus agalactiae	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	2	(2.8)	1	(2.0)	0	(0.0)
Streptococcus milleri	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Streptococcus viridans	1	(9.1)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.4)	2	(4.1)	1	(2.9)
gram-positive aerobic bacilli	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Corynebacterium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative aerobic bacilli	2	(18.2)	5	(26.3)	3	(14.3)	5	(18.5)	8	(18.6)	5	(7.0)	4	(8.2)	8	(23.5)
Acinetobacter baumannii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Aeromonas hydrophila	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Enterobacter aerogenes	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Enterobacter cloacae	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Escherichia coli	1	(9.1)	2	(10.5)	1	(4.8)	0	(0.0)	2	(4.7)	0	(0.0)	3	(6.1)	5	(14.7)
Klebsiella pneumoniae	0	(0.0)	1	(5.3)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)

Table 7: continued

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem		Cefotetan		Ertapenem		Cefotetan		Ertapenem		Cefotetan		Ertapenem		Cefotetan	
	(N=338)		(N=334)		(N=338)		(N=334)		(N=338)		(N=334)		(N=338)		(N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Morganella morganii	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Proteus mirabilis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(7.0)	1	(1.4)	0	(0.0)	0	(0.0)
Pseudomonas	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pseudomonas aeruginosa	0	(0.0)	0	(0.0)	1	(4.8)	2	(7.4)	2	(4.7)	4	(5.6)	0	(0.0)	1	(2.9)
gram-positive anaerobic cocci	0	(0.0)	1	(5.3)	1	(4.8)	0	(0.0)	3	(7.0)	2	(2.8)	1	(2.0)	1	(2.9)
Anaerococcus prevotii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Peptostreptococcus anaerobius	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	1	(2.9)
Peptostreptococcus magnus	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	2	(4.7)	0	(0.0)	0	(0.0)	0	(0.0)
Peptostreptococcus micros	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Ruminococcus hansenii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
gram-positive anaerobic bacilli	0	(0.0)	2	(10.5)	5	(23.8)	2	(7.4)	5	(11.6)	20	(28.2)	10	(20.4)	2	(5.9)
Bifidobacterium catenulatum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	1	(2.0)	0	(0.0)
Clostridium clostridiiforme	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium difficile	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium hastiforme	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem		Cefotetan		Ertapenem		Cefotetan		Ertapenem		Cefotetan		Ertapenem		Cefotetan	
	(N=338)		(N=334)		(N=338)		(N=334)		(N=338)		(N=334)		(N=338)		(N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Clostridium innocuum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	7	(9.9)	1	(2.0)	1	(2.9)
Clostridium nexile	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
Clostridium perfringens	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Clostridium ramosum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	1	(1.4)	0	(0.0)	0	(0.0)
Eubacterium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	1	(1.4)	2	(4.1)	1	(2.9)
Eubacterium biforme	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Eubacterium lentum	0	(0.0)	0	(0.0)	1	(4.8)	1	(3.7)	1	(2.3)	7	(9.9)	1	(2.0)	0	(0.0)
Eubacterium limosum	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eubacterium tortuosum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Lactobacillus plantarum	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	0	(0.0)	1	(2.0)	0	(0.0)
Propionibacterium acnes	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
gram-positive anaerobic bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
gram-negative anaerobic cocci	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Acidaminococcus fermentans	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Veillonella	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 7: continued

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
gram-negative anaerobic bacilli	2	(18.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.8)	5	(10.2)	0	(0.0)
Desulfovibrio fairfieldensis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Porphyromonas asaccharolytica	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
Porphyromonas cangingivalis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Prevotella intermedia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Sutterella wadsworthensis	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative anaerobic bacillus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.1)	0	(0.0)
gram-negative anaerobic coccobacilli	4	(36.4)	4	(21.1)	7	(33.3)	4	(14.8)	5	(11.6)	21	(29.6)	13	(26.5)	11	(32.4)
Bacteroides caccae	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Bacteroides capillosus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
Bacteroides distasonis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(5.6)	1	(2.0)	0	(0.0)
Bacteroides fragilis	1	(9.1)	3	(15.8)	3	(14.3)	2	(7.4)	3	(7.0)	4	(5.6)	2	(4.1)	3	(8.8)
Bacteroides merdae	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)	1	(2.9)
Bacteroides ovatus	1	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.8)	2	(4.1)	1	(2.9)
Bacteroides sp.	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Bacteroides stercoris	1	(9.1)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Bacteroides thetaiotaomicron	1	(9.1)	0	(0.0)	1	(4.8)	0	(0.0)	1	(2.3)	8	(11.3)	2	(4.1)	2	(5.9)

	Organ/space				Deep incisional				Superficial incisional				Anastomotic Leak			
	Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)		Ertapenem (N=338)		Cefotetan (N=334)	
	n=3		n=7		n=5		n=11		n=17		n=28		n=5		n=9	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Bacteroides uniformis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	1	(1.4)	1	(2.0)	1	(2.9)
Bacteroides vulgatus	0	(0.0)	1	(5.3)	2	(9.5)	1	(3.7)	0	(0.0)	1	(1.4)	2	(4.1)	0	(0.0)
Fusobacterium mortiferum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Fusobacterium russii	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
Fusobacterium varium	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative bacilli	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
gram-negative bacillus	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.4)	0	(0.0)	0	(0.0)	1	(2.0)	0	(0.0)
bacterial organisms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Bacteria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)

† Isolates obtained from surgical site infection or anastomotic leak failures.

The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.

N = Number of evaluable patients in each treatment group.

n = Number of patients with a documented pathogen from each source category in each treatment group.

m = Number of documented pathogens.

% = Number of documented pathogens / all pathogens.

A review of the most frequently isolated pathogens reveals no strong evidence of a relationship between type of surgical infection and pathogens isolated. Enterococci and *Enterococcus faecalis* were seen in a slightly higher number in superficial incisional and organ/space infection in the cefotetan group but were evenly distributed across infection type in the ertapenem group. *Staphylococcus aureus* was isolated most frequently in superficial incision infection in both groups and *Escherichia coli* were seen most frequently in patients with an anastomotic leak in both groups.

Bacteroides fragilis appear evenly distributed across each treatment groups. However, *Bacteroides thetaiotaomicron* was seen most frequently in superficial incision infections

in the cefotetan group [(8/10) compared with 1/5 for the ertapenem treatment group)] and evenly distributed across infection type in the ertapenem group (Table 8 and 9). *Clostridium innocuum* and *Eubacterium lentum* isolated in the cefotetan group were isolated from superficial incision infections. There were a higher number of *C. innocuum* in the cefotetan treatment group compared to the ertapenem group; furthermore, there were higher incidences of *C. innocuum*-associated superficial infections in the cefotetan treatment group. Anaerobes were most frequently associated with superficial infection (57%) in the cefotetan treatment group compared with 19.14% in the ertapenem treatment group. In the ertapenem treatment group, the major source of anaerobes was from anastomotic leak (51.06%) in the ertapenem treatment group, compared with approximately 23% in the cefotetan treatment group. The significances of this finding are not known.

Table 8: Ertapenem treatment group (Evaluable population)

Pathogen: Anaerobes (N)	Source (n)			
	Superficial infection	Anastomotic Leak	Deep incision	Organ Space
B. fragilis (10)	3	2	4	1
B. thetaiotaomicron (5)	1	2	1	1
B. distasonis (2)	—	2	—	—
B. caccae (1)	—	1	—	—
B. merdae (1)	—	1	—	—
B. ovatus (4)	—	3	—	1
B. stercoris (1)	—	—	—	1
B. uniformis (4)	1	3	—	—
B. vulgatus (4)	—	2	2	—
Clostridium spp. (1)	—	1	—	—
C. difficile (2)	—	2	—	—
C. hastiforme (1)	1	—	—	—
C. innocuum (2)	—	2	—	—
C. ramosum (2)	1	—	1	—
E. lentum (3)	1	1	1	—
Eubacterium spp. (4)	1	2	1	—
Total: 47	9/47 (19.14%)	24/47 (51.06%)	10/47 (21.27%)	4/47 (8.50%)

Table 9: Cefotetan treatment group:

Pathogen: Anaerobes (N)	Source (n)			
	Superficial infection	Anastomotic Leak	Deep incisional	Organ Space
B. fragilis (13)	4	3	3	3
B. thetaiotaomicron (10)	8	2	—	—
B. distasonis (4)	3	1	—	—
B. merdae (1)	—	1	—	—
B. ovatus (4)	2	1	—	1
B. stercoris (2)	1	—	1	—
B. uniformis (2)	1	1	—	—
B. vulgatus (3)	1	0	1	1
Bacteroides spp	—	1	—	—
Clostridium spp. (1)	—	1	—	—
C. difficile (2)	—	2	—	—
C. clostridiiforme(1)	—	—	—	1
C. innocuum (8)	7	1	—	—
C. ramosum (1)	1	—	—	—
E. lentum (8)	7	—	1	—
Total: 61	35/61 (57.38%)	14/61 (22.95%)	6/61 (9.84%)	6/61 (9.84%)

Aerobic specimens were processed by the local microbiology laboratories associated with each study site and anaerobic specimens were handled by the central laboratory (b) (4) Anaerobic data from the central laboratory was used for the summaries. If the local laboratory reported anaerobic data, those pathogens were displayed if the central laboratory did not receive a specimen for analysis. The sponsor states that in vitro susceptibility testing was performed on all pathogens identified by the investigator. The in vitro MIC susceptibility results for the pathogens isolated from surgical site infections in the evaluable populations are displayed in separate tables for the two treatment groups; the ertapenem group in Table 10 and the cefotetan group in Table 11.

Table 10: In Vitro MIC Susceptibility of Documented Pathogens Ertapenem Treatment Group --- Surgical Source† (Evaluable Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	42	21	24	8	33.3	2	8.3	14	58.3	24	6	25.0	0	0.0	18	75.0
Abiotrophia	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Enterococcus	8	7	5	1	20.0	0	0.0	4	80.0	5	1	20.0	0	0.0	4	80.0
Enterococcus avium	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus durans	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus faecalis	4	4	2	0	0.0	0	0.0	2	100.0	2	0	0.0	0	0.0	2	100.0
Enterococcus faecium	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus raffinosus	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus	4	4	3	2	66.7	0	0.0	1	33.3	3	0	0.0	0	0.0	3	100.0
Staphylococcus aureus	9	9	7	4	57.1	2	28.6	1	14.3	7	4	57.1	0	0.0	3	42.9
Staphylococcus aureus MRSA[††]	2	2	2	0	0.0	2	100.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Staphylococcus aureus MSSA[††]	4	4	3	3	100.0	0	0.0	0	0.0	3	2	66.7	0	0.0	1	33.3
Staphylococcus aureus Non Spec[††]	3	3	2	1	50.0	0	0.0	1	50.0	2	2	100.0	0	0.0	0	0.0
Staphylococcus epidermidis	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus sciuri	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Streptococcus	4	4	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Streptococcus agalactiae	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus milleri	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus viridans	3	3	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-positive aerobic bacilli	3	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Bacillus	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Corynebacterium	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative aerobic bacilli	17	14	11	10	90.9	0	0.0	1	9.1	11	9	81.8	0	0.0	2	18.2
Acinetobacter baumannii	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterobacter cloacae	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Escherichia coli	7	7	5	5	100.0	0	0.0	0	0.0	5	5	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Proteus mirabilis	3	3	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Pseudomonas	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Pseudomonas aeruginosa	3	3	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0

Table 10: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive anaerobic cocci	5	4	5	5	100.0	0	0.0	0	0.0	5	5	100.0	0	0.0	0	0.0
Anaerococcus prevotii	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Peptostreptococcus magnus	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Peptostreptococcus micros	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
gram-positive anaerobic bacilli	20	9	19	18	94.7	1	5.3	0	0.0	19	11	57.9	3	15.8	5	26.3
Bifidobacterium catenulatum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium difficile	1	1	1	0	0.0	1	100.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Clostridium hastiforme	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium innocuum	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Clostridium nexile	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium perfringens	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium ramosum	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Eubacterium	3	2	3	3	100.0	0	0.0	0	0.0	3	3	100.0	0	0.0	0	0.0
Eubacterium lentum	3	3	3	3	100.0	0	0.0	0	0.0	3	0	0.0	1	33.3	2	66.7

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Lactobacillus plantarum	3	3	3	3	100.0	0	0.0	0	0.0	3	1	33.3	1	33.3	1	33.3
gram-positive anaerobic bacillus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative anaerobic bacilli	7	5	5	5	100.0	0	0.0	0	0.0	5	4	80.0	0	0.0	1	20.0
Porphyromonas asaccharolytica	3	3	3	3	100.0	0	0.0	0	0.0	3	3	100.0	0	0.0	0	0.0
Porphyromonas cangingivalis	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Sutterella wadsworthensis	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
gram-negative anaerobic bacillus	2	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative anaerobic coccobacilli	29	12	28	28	100.0	0	0.0	0	0.0	28	10	35.7	2	7.1	16	57.1
Bacteroides caccae	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides capillosus	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Bacteroides distasonis	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides fragilis	9	9	8	8	100.0	0	0.0	0	0.0	8	5	62.5	1	12.5	2	25.0
Bacteroides merdae	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Bacteroides ovatus	3	2	3	3	100.0	0	0.0	0	0.0	3	0	0.0	0	0.0	3	100.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Bacteroides stercoris	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides thetaiotaomicron	5	5	5	5	100.0	0	0.0	0	0.0	5	0	0.0	0	0.0	5	100.0
Bacteroides uniformis	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Bacteroides vulgatus	4	4	4	4	100.0	0	0.0	0	0.0	4	3	75.0	0	0.0	1	25.0
Fusobacterium varium	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative bacilli	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative bacillus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

† Isolates obtained from surgical site infection or anastomotic leak failures.

†† Staphylococcus aureus MRSA (Methicillin-Resistant Staphylococcus aureus), MSSA (Methicillin-Sensitive Staphylococcus aureus) and Non Spec (Non Specified Staphylococcus aureus) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

Table 11: In Vitro MIC Susceptibility of Documented Pathogens-Cefotetan Treatment Group - Surgical Source† (Evaluable Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	51	34	24	9	37.5	1	4.2	14	58.3	24	5	20.8	0	0.0	19	79.2
Enterococcus	11	11	6	0	0.0	0	0.0	6	100.0	6	0	0.0	0	0.0	6	100.0
Enterococcus avium	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterococcus faecalis	10	9	6	0	0.0	1	16.7	5	83.3	5	0	0.0	0	0.0	5	100.0
Enterococcus faecium	3	3	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterococcus gallinarum	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus sp.	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Staphylococcus	3	3	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Staphylococcus aureus	10	10	5	4	100.0	0	0.0	1	100.0	6	2	33.3	0	0.0	4	66.7
Staphylococcus aureus MRSA††	2	2	1	0	0.0	0	0.0	1	100.0	2	0	0.0	0	0.0	2	100.0
Staphylococcus aureus MSSA††	3	3	3	3	100.0	0	0.0	0	0.0	3	2	66.7	0	0.0	1	33.3
Staphylococcus aureus Non Spec††	5	5	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus epidermidis	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus	3	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus agalactiae	4	4	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Streptococcus viridans	3	3	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0

Table 11: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-negative aerobic bacilli	23	18	10	9	90.0	0	0.0	1	10.0	15	6	40.0	1	6.7	8	53.3
Aeromonas hydrophila	1	1	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterobacter aerogenes	2	2	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterobacter cloacae	1	1	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Escherichia coli	7	7	2	2	100.0	0	0.0	0	0.0	4	4	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	2	2	2	2	100.0	0	0.0	0	0.0	2	1	50.0	1	50.0	0	0.0
Morganella morganii	2	2	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Proteus mirabilis	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Pseudomonas aeruginosa	7	7	4	3	75.0	0	0.0	1	25.0	4	0	0.0	0	0.0	4	100.0
gram-positive anaerobic cocci	4	4	4	4	100.0	0	0.0	0	0.0	4	1	25.0	1	25.0	2	50.0
Peptostreptococcus anaerobius	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	1	50.0	1	50.0
Peptostreptococcus magnus	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Ruminococcus hansenii	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive anaerobic bacilli	26	15	25	24	96.0	1	4.0	0	0.0	25	7	28.0	1	4.0	17	68.0
Clostridium	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Clostridium clostridiiforme	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium innocuum	8	8	8	7	87.5	1	12.5	0	0.0	8	0	0.0	0	0.0	8	100.0
Clostridium ramosum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Eubacterium	2	2	2	2	100.0	0	0.0	0	0.0	2	1	50.0	0	0.0	1	50.0
Eubacterium biforme	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Eubacterium lentum	8	8	8	8	100.0	0	0.0	0	0.0	8	0	0.0	0	0.0	8	100.0
Eubacterium limosum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Eubacterium tortuosum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Propionibacterium acnes	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
gram-negative anaerobic cocci	2	2	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Acidaminococcus fermentans	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Veillonella	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-negative anaerobic bacilli	2	2	2	1	50.0	0	0.0	1	50.0	2	1	50.0	0	0.0	1	50.0
Desulfovibrio fairfieldensis	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Prevotella intermedia	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative anaerobic coccobacilli	40	27	34	34	100.0	0	0.0	0	0.0	34	8	23.5	3	8.8	23	67.6
Bacteroides distasonis	4	4	4	4	100.0	0	0.0	0	0.0	4	1	25.0	1	25.0	2	50.0
Bacteroides fragilis	12	12	8	8	100.0	0	0.0	0	0.0	8	4	50.0	0	0.0	4	50.0
Bacteroides merdae	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Bacteroides ovatus	3	3	3	3	100.0	0	0.0	0	0.0	3	0	0.0	0	0.0	3	100.0
Bacteroides sp.	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Bacteroides stercoris	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Bacteroides thetaiotaomicron	10	10	9	9	100.0	0	0.0	0	0.0	9	0	0.0	0	0.0	9	100.0
Bacteroides uniformis	2	2	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides vulgatus	3	3	3	3	100.0	0	0.0	0	0.0	3	1	33.3	0	0.0	2	66.7
Fusobacterium mortiferum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Fusobacterium russii	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0

Table 11: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-negative bacilli	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative bacillus	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
bacterial organisms	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Bacteria	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

† Isolates obtained from surgical site infection or anastomotic leak failures.

†† Staphylococcus aureus MRSA (Methicillin-Resistant Staphylococcus aureus), MSSA (Methicillin-Sensitive Staphylococcus aureus) and Non Spec (Non Specified Staphylococcus aureus) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

Enterococcus *(avium, durans, faecalis, faecium, raffinosus)* isolated from patients treated with ertapenem as well as those treated with cefotetan exhibited a high prevalence of resistance to both study drugs. In addition, methicillin resistant *Staphylococcus aureus* isolated from patients in each group was also resistant to both study drugs. *Escherichia coli* identified the study were susceptible to both study drugs. All species of *Bacteroides* identified were susceptible to ertapenem but showed varying levels of resistance to cefotetan. Additionally, *Clostridium innocuum* and *Eubacterium lentum* were generally susceptible to ertapenem but generally resistant to cefotetan.

Overall, the majority of pathogens (66.7%) isolated and tested in the cefotetan group were resistant to cefotetan, whereas only 16.3% of the isolates tested in the ertapenem group were resistant to ertapenem. Figures 1 and 2 show the frequency distributions according to MIC for anaerobes in the evaluable population (Protocol 039) for cefotetan and ertapenem, respectively. The majority of the anaerobic isolates were susceptible to ertapenem (MIC $\leq$ 2 µg/mL but resistant to cefotetan (MIC $\geq$ 64 µg/mL).

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Figure 1: Frequency Distribution of Cefotetan Minimum Inhibitory Concentrations (MICs) for Anaerobes in Evaluable Patients treated with Cefotetan (Protocol 039)

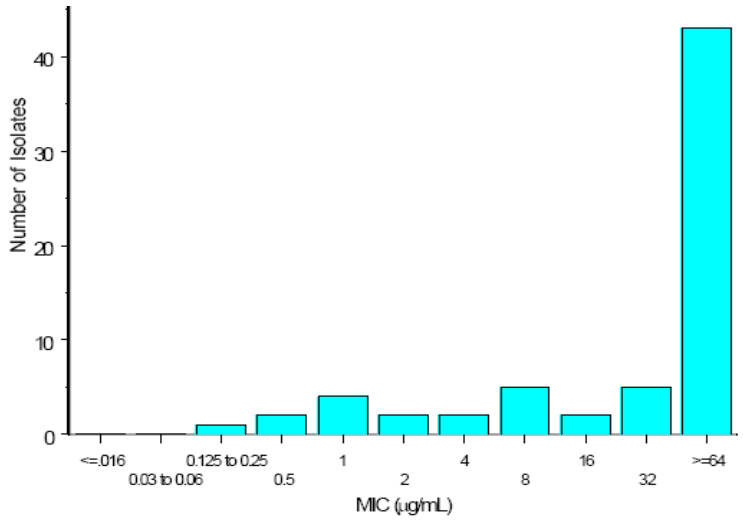
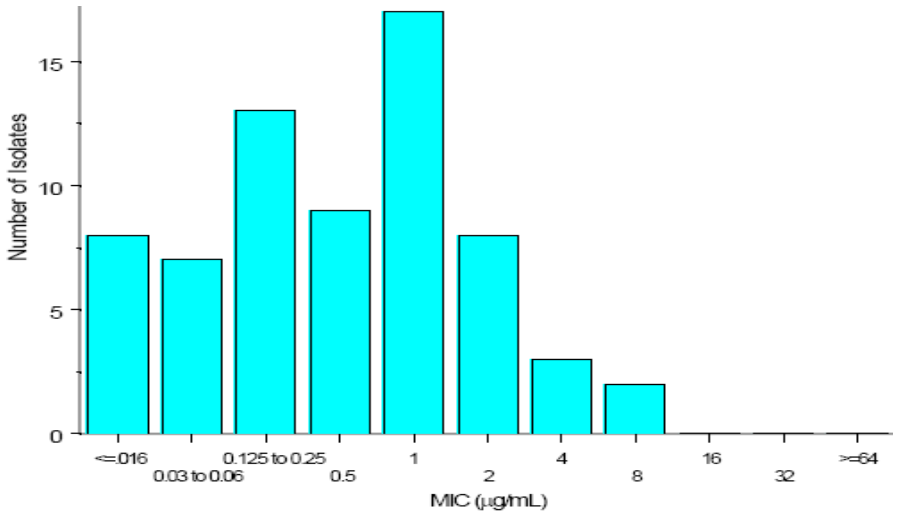


Figure 2: Frequency Distribution of Ertapenem Minimum Inhibitory Concentrations (MICs) for Anaerobes in Evaluable Patients treated with Ertapenem (Protocol 039)



Conclusions:

The frequency distributions of ertapenem MIC and cefotetan MIC for the anaerobes show that the majority of the isolates were resistant to cefotetan but susceptible to ertapenem.

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

Microbiology of Failures:

The number (%) of documented pathogens from the surgical site is summarized by treatment group for the MITT qualified population in Table 12. The pathogens identified are similar to those seen in the evaluable population.

Table 12: Documented Pathogens – Surgical Source† (MITT Qualified Population)

	Ertapenem (N=451) n=37 m (%)	Cefotetan (N=450) n=64 m (%)
All Documented Pathogens	143	183
gram-positive aerobic cocci	48 (33.6)	59 (32.1)
Abiotrophia	1 (0.7)	0 (0.0)
Enterococcus	9 (6.3)	12 (6.5)
Enterococcus avium	1 (0.7)	1 (0.5)
Enterococcus durans	1 (0.7)	0 (0.0)
Enterococcus faecalis	6 (4.2)	11 (6.0)
Enterococcus faecium	1 (0.7)	4 (2.2)
Enterococcus gallinarum	0 (0.0)	1 (0.5)
Enterococcus raffinosus	1 (0.7)	0 (0.0)
Enterococcus sp.	0 (0.0)	1 (0.5)
Granulicatella adiacens	0 (0.0)	1 (0.5)
Staphylococcus	6 (4.2)	3 (1.6)
Staphylococcus aureus	10 (7.0)	12 (6.5)
Staphylococcus aureus MRSA	3 (2.1)	3 (1.6)
Staphylococcus aureus MSSA	4 (2.8)	4 (2.2)
Staphylococcus aureus Non Spec	3 (2.1)	5 (2.7)
Staphylococcus epidermidis	1 (0.7)	1 (0.5)
Staphylococcus sciuri	1 (0.7)	0 (0.0)
Streptococcus	4 (2.8)	5 (2.7)
Streptococcus agalactiae	1 (0.7)	4 (2.2)
Streptococcus milleri	2 (1.4)	0 (0.0)
Streptococcus viridans	3 (2.1)	3 (1.6)
gram-positive aerobic bacilli	3 (2.1)	0 (0.0)
Bacillus	2 (1.4)	0 (0.0)
Corynebacterium	1 (0.7)	0 (0.0)
gram-negative aerobic bacilli	21 (14.7)	28 (15.2)
Acinetobacter baumannii	1 (0.7)	0 (0.0)
Aeromonas hydrophila	0 (0.0)	1 (0.5)
Enterobacter aerogenes	0 (0.0)	2 (1.1)
Enterobacter cloacae	1 (0.7)	1 (0.5)
Escherichia coli	9 (6.3)	9 (4.9)
Klebsiella pneumoniae	2 (1.4)	2 (1.1)
Morganella morganii	0 (0.0)	2 (1.1)

Table 12: continued

	Ertapenem (N=451) n=37 m (%)	Cefotetan (N=450) n=64 m (%)
Proteus mirabilis	3 (2.1)	1 (0.5)
Pseudomonas	1 (0.7)	0 (0.0)
Pseudomonas aeruginosa	4 (2.8)	10 (5.4)
gram-negative aerobic coccobacilli	0 (0.0)	1 (0.5)
Eikenella corrodens	0 (0.0)	1 (0.5)
gram-positive anaerobic cocci	5 (3.5)	5 (2.7)
Anaerococcus prevotii	1 (0.7)	0 (0.0)
Peptostreptococcus anaerobius	0 (0.0)	2 (1.1)
Peptostreptococcus magnus	2 (1.4)	1 (0.5)
Peptostreptococcus micros	2 (1.4)	1 (0.5)
Ruminococcus hansenii	0 (0.0)	1 (0.5)
gram-positive anaerobic bacilli	21 (14.7)	31 (16.8)
Actinomyces odontolyticus	0 (0.0)	1 (0.5)
Bifidobacterium catenulatum	1 (0.7)	0 (0.0)
Clostridium	1 (0.7)	1 (0.5)
Clostridium clostridiiforme	0 (0.0)	1 (0.5)
Clostridium difficile	1 (0.7)	0 (0.0)
Clostridium hastiforme	1 (0.7)	0 (0.0)
Clostridium innocuum	2 (1.4)	9 (4.9)
Clostridium nexile	1 (0.7)	0 (0.0)
Clostridium perfringens	1 (0.7)	0 (0.0)
Clostridium ramosum	3 (2.1)	2 (1.1)
Eubacterium	3 (2.1)	3 (1.6)
Eubacterium biforme	0 (0.0)	1 (0.5)
Eubacterium lentum	3 (2.1)	9 (4.9)
Eubacterium limosum	0 (0.0)	1 (0.5)
Eubacterium tortuosum	0 (0.0)	1 (0.5)
Lactobacillus plantarum	3 (2.1)	0 (0.0)
Propionibacterium acnes	0 (0.0)	2 (1.1)
gram-positive anaerobic bacillus	1 (0.7)	0 (0.0)
gram-negative anaerobic cocci	0 (0.0)	3 (1.6)
Acidaminococcus fermentans	0 (0.0)	1 (0.5)
Veillonella	0 (0.0)	2 (1.1)
gram-negative anaerobic bacilli	9 (6.3)	2 (1.1)
Bilophila wadsworthia	1 (0.7)	0 (0.0)

Table 12: continued

	Ertapenem (N=451) n=37 m (%)	Cefotetan (N=450) n=64 m (%)
Desulfovibrio fairfieldensis	0 (0.0)	1 (0.5)
Porphyromonas asaccharolytica	3 (2.1)	0 (0.0)
Porphyromonas cangingivalis	1 (0.7)	0 (0.0)
Prevotella bivia	1 (0.7)	0 (0.0)
Prevotella intermedia	0 (0.0)	1 (0.5)
Sutterella wadsworthensis	1 (0.7)	0 (0.0)
gram-negative anaerobic bacillus	2 (1.4)	0 (0.0)
gram-negative anaerobic coccobacilli	35 (24.5)	51 (27.7)
Bacteroides caccae	1 (0.7)	0 (0.0)
Bacteroides capillosus	1 (0.7)	0 (0.0)
Bacteroides distasonis	3 (2.1)	5 (2.7)
Bacteroides fragilis	10 (7.0)	16 (8.7)
Bacteroides merdae	1 (0.7)	2 (1.1)
Bacteroides ovatus	4 (2.8)	3 (1.6)
Bacteroides sp.	0 (0.0)	1 (0.5)
Bacteroides stercoris	1 (0.7)	2 (1.1)
Bacteroides thetaiotaomicron	6 (4.2)	13 (7.1)
Bacteroides uniformis	2 (1.4)	4 (2.2)
Bacteroides vulgatus	5 (3.5)	3 (1.6)
Fusobacterium mortiferum	0 (0.0)	1 (0.5)
Fusobacterium russii	0 (0.0)	1 (0.5)
Fusobacterium varium	1 (0.7)	0 (0.0)
gram-negative bacilli	1 (0.7)	2 (1.1)
gram-negative bacillus	1 (0.7)	2 (1.1)
bacterial organisms	0 (0.0)	1 (0.5)
Bacteria	0 (0.0)	1 (0.5)

† Isolates obtained from surgical site infection or anastomotic leak failures.
The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.
N = Number of MITT Qualified patients in each treatment group.
n = Number of patients with a documented pathogen from each source category in each treatment group.
m = Number of documented pathogens.
% = Number of documented pathogens/all pathogens.

The in vitro susceptibility results for the pathogens from the surgical site for the MITT qualified population are displayed in separate tables for the two treatment groups; the ertapenem group in Table 13 and the cefotetan group in Table 14. Susceptibility results were consistent with those seen in the evaluable population.

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Table 13: In Vitro MIC Susceptibility of Documented Pathogens- Ertapenem Treatment Group Surgical Source† (MITT Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	48	26	25	8	32.0	2	8.0	15	60.0	25	6	24.0	0	0.0	19	76.0
Abiotrophia	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Enterococcus	9	8	5	1	20.0	0	0.0	4	80.0	5	1	20.0	0	0.0	4	80.0
Enterococcus avium	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus durans	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus faecalis	6	6	3	0	0.0	0	0.0	3	100.0	3	0	0.0	0	0.0	3	100.0
Enterococcus faecium	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus raffinosus	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus	6	6	3	2	66.7	0	0.0	1	33.3	3	0	0.0	0	0.0	3	100.0
Staphylococcus aureus	10	10	7	4	57.1	2	28.6	1	14.3	7	4	57.1	0	0.0	3	42.9
Staphylococcus aureus MRSA††	3	3	2	0	0.0	2	100.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Staphylococcus aureus MSSA††	4	4	3	3	100.0	0	0.0	0	0.0	3	2	66.7	0	0.0	1	33.3
Staphylococcus aureus Non Spec††	3	3	2	1	50.0	0	0.0	1	50.0	2	2	100.0	0	0.0	0	0.0
Staphylococcus epidermidis	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus sciuri	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Streptococcus	4	4	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Streptococcus agalactiae	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus milleri	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus viridans	3	3	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-positive aerobic bacilli	3	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Bacillus	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Corynebacterium	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative aerobic bacilli	21	16	11	10	90.9	0	0.0	1	9.1	11	9	81.8	0	0.0	2	18.2
Acinetobacter baumannii	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterobacter cloacae	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Escherichia coli	9	9	5	5	100.0	0	0.0	0	0.0	5	5	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	2	2	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Proteus mirabilis	3	3	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Pseudomonas	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Pseudomonas aeruginosa	4	4	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0

Table 13: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive anaerobic cocci	5	4	5	5	100.0	0	0.0	0	0.0	5	5	100.0	0	0.0	0	0.0
Anaerococcus prevotii	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Peptostreptococcus magnus	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Peptostreptococcus micros	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
gram-positive anaerobic bacilli	21	10	20	19	95.0	1	5.0	0	0.0	20	12	60.0	3	15.0	5	25.0
Bifidobacterium catenulatum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium difficile	1	1	1	0	0.0	1	100.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Clostridium hastiforme	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium innocuum	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Clostridium nexile	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium perfringens	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium ramosum	3	3	3	3	100.0	0	0.0	0	0.0	3	3	100.0	0	0.0	0	0.0
Eubacterium	3	2	3	3	100.0	0	0.0	0	0.0	3	3	100.0	0	0.0	0	0.0
Eubacterium lentum	3	3	3	3	100.0	0	0.0	0	0.0	3	0	0.0	1	33.3	2	66.7

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Lactobacillus plantarum	3	3	3	3	100.0	0	0.0	0	0.0	3	1	33.3	1	33.3	1	33.3
gram-positive anaerobic bacillus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative anaerobic bacilli	9	6	7	7	100.0	0	0.0	0	0.0	7	6	85.7	0	0.0	1	14.3
Bilophila wadsworthia	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Porphyromonas asaccharolytica	3	3	3	3	100.0	0	0.0	0	0.0	3	3	100.0	0	0.0	0	0.0
Porphyromonas cangingivalis	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Prevotella bivia	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Sutterella wadsworthensis	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
gram-negative anaerobic bacillus	2	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative anaerobic coccobacilli	35	15	34	34	100.0	0	0.0	0	0.0	34	12	35.3	4	11.8	18	52.9
Bacteroides caccae	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides capillosus	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Bacteroides distasonis	3	3	3	3	100.0	0	0.0	0	0.0	3	0	0.0	1	33.3	2	66.7
Bacteroides fragilis	10	10	9	9	100.0	0	0.0	0	0.0	9	6	66.7	1	11.1	2	22.2
Bacteroides merdae	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Bacteroides ovatus	4	3	4	4	100.0	0	0.0	0	0.0	4	0	0.0	0	0.0	4	100.0
Bacteroides stercoris	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Bacteroides thetaiotaomicron	6	6	6	6	100.0	0	0.0	0	0.0	6	0	0.0	1	16.7	5	83.3
Bacteroides uniformis	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Bacteroides vulgatus	5	5	5	5	100.0	0	0.0	0	0.0	5	4	80.0	0	0.0	1	20.0
Fusobacterium varium	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative bacilli	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative bacillus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

† Isolates obtained from surgical site infection or anastomotic leak failures.

†† Staphylococcus aureus MRSA (Methicillin-Resistant Staphylococcus aureus), MSSA (Methicillin-Sensitive Staphylococcus aureus) and Non Spec (Non Specified Staphylococcus aureus) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

Table 14: In Vitro MIC Susceptibility of Documented Pathogens- Cefotetan Treatment Group Surgical Source†(MITT Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	59	40	29	10	34.5	1	3.4	18	62.1	29	6	20.7	0	0.0	23	75.0
Enterococcus	12	12	7	0	0.0	0	0.0	7	100.0	7	0	0.0	0	0.0	7	100.0
Enterococcus avium	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterococcus faecalis	11	10	7	0	0.0	1	14.3	6	85.7	6	0	0.0	0	0.0	6	100.0
Enterococcus faecium	4	4	2	1	50.0	0	0.0	1	50.0	2	0	0.0	0	0.0	2	100.0
Enterococcus gallinarum	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Enterococcus sp.	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Granulicatella adiacens	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Staphylococcus	3	3	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Staphylococcus aureus	12	12	6	4	66.7	0	0.0	2	33.3	7	2	28.6	0	0.0	5	57.1
Staphylococcus aureus MRSA††	3	3	2	0	0.0	0	0.0	2	100.0	3	0	0.0	0	0.0	3	100.0
Staphylococcus aureus MSSA††	4	4	3	3	100.0	0	0.0	0	0.0	3	2	66.7	0	0.0	1	33.3
Staphylococcus aureus Non Spec††	5	5	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus epidermidis	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

Table 14: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Streptococcus	5	4	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus agalactiae	4	4	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Streptococcus viridans	3	3	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
gram-negative aerobic bacilli	28	22	14	12	85.7	0	0.0	2	14.3	20	8	40.0	1	5.0	11	55.0
Aeromonas hydrophila	1	1	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterobacter aerogenes	2	2	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Enterobacter cloacae	1	1	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Escherichia coli	9	9	3	3	100.0	0	0.0	0	0.0	6	6	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	2	2	2	2	100.0	0	0.0	0	0.0	2	1	50.0	1	50.0	0	0.0
Morganella morganii	2	2	0	0	0.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Proteus mirabilis	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Pseudomonas aeruginosa	10	10	7	5	71.4	0	0.0	2	28.6	7	0	0.0	0	0.0	7	100.0
gram-negative aerobic coccobacilli	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Eikenella corrodens	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive anaerobic cocci	5	5	5	5	100.0	0	0.0	0	0.0	5	2	40.0	1	20.0	2	40.0
Peptostreptococcus anaerobius	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	1	50.0	1	50.0
Peptostreptococcus magnus	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Peptostreptococcus micros	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Ruminococcus hansenii	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
gram-positive anaerobic bacilli	31	17	30	29	96.7	1	3.3	0	0.0	30	10	33.3	1	3.3	19	63.3
Actinomyces odontolyticus	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Clostridium clostridiiforme	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Clostridium innocuum	9	9	9	8	88.9	1	11.1	0	0.0	9	0	0.0	0	0.0	9	100.0
Clostridium ramosum	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Eubacterium	3	3	3	3	100.0	0	0.0	0	0.0	3	2	66.7	0	0.0	1	33.3
Eubacterium biforme	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Eubacterium lentum	9	9	9	9	100.0	0	0.0	0	0.0	9	0	0.0	0	0.0	9	100.0
Eubacterium limosum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0

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Table 14: continued

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
Eubacterium tortuosum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Propionibacterium acnes	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
gram-negative anaerobic cocci	3	3	2	2	100.0	0	0.0	0	0.0	2	1	50.0	1	50.0	0	0.0
Acidaminococcus fermentans	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Veillonella	2	2	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
gram-negative anaerobic bacilli	2	2	2	1	50.0	0	0.0	1	50.0	2	1	50.0	0	0.0	1	50.0
Desulfovibrio fairfieldensis	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Prevotella intermedia	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative anaerobic coccobacilli	51	34	44	44	100.0	0	0.0	0	0.0	44	11	25.0	4	9.1	29	65.9
Bacteroides distasonis	5	5	5	5	100.0	0	0.0	0	0.0	5	1	20.0	1	20.0	3	60.0
Bacteroides fragilis	16	16	11	11	100.0	0	0.0	0	0.0	11	7	63.6	0	0.0	4	36.4
Bacteroides merdae	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	2	100.0	0	0.0
Bacteroides ovatus	3	3	3	3	100.0	0	0.0	0	0.0	3	0	0.0	0	0.0	3	100.0
Bacteroides sp.	1	1	1	1	100.0	0	0.0	0	0.0	1	0	0.0	1	100.0	0	0.0
Bacteroides stercoris	2	2	2	2	100.0	0	0.0	0	0.0	2	0	0.0	0	0.0	2	100.0
Bacteroides thetaiotaomicron	13	13	12	12	100.0	0	0.0	0	0.0	12	0	0.0	0	0.0	12	100.0
Bacteroides uniformis	4	4	3	3	100.0	0	0.0	0	0.0	3	0	0.0	0	0.0	3	100.0
Bacteroides vulgatus	3	3	3	3	100.0	0	0.0	0	0.0	3	1	33.3	0	0.0	2	66.7
Fusobacterium mortiferum	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Fusobacterium russii	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative bacilli	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative bacillus	2	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
bacterial organisms	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Bacteria	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

† Isolates obtained from surgical site infection or anastomotic leak failures.

†† Staphylococcus aureus MRSA (Methicillin-Resistant Staphylococcus aureus), MSSA (Methicillin-Sensitive Staphylococcus aureus) and Non Spec (Non Specified Staphylococcus aureus) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

Distant Site Infection:

The estimated proportions of patients with any distant site infection and by specific type of distant site infection (Pneumonia, Urinary Tract Infection, Vascular Site Infection, Other) are summarized in Table 15 for the MITT population. The differences in the incidence of distant site infections (overall and by specific type) and corresponding 95% confidence intervals are also displayed.

All patients with a reported distant site infection are summarized in Table 15, regardless of the patients' clinical outcome from the surgical site. Therefore, Table 15 includes evaluable failures who reported distant site infections. Although a patient could have more than one distant site infection, they are only counted once in the any distant site infection category. Some examples of "Other" distant site infections include *Clostridium*

difficile infection, respiratory tract infections, and blood infections.
Although the overall incidence of distant site infections was similar across treatment groups (10.6% ertapenem and 12.3% cefotetan) the incidence of specific types of infections varied across treatment. Cefotetan had a numerically higher incidence of pneumonia and UTI while ertapenem had a numerically higher incidence of distant site infections categorized as other.

Two patients had non-serious adverse experiences of pneumonia but no clinical response of distant site infection, pneumonia was reported. AN2028 and AN2224, both in the cefotetan treatment group, had pneumonia reported as an adverse event. However, these patients received no antimicrobial therapy for the pneumonia and the clinical response for both of these patients was failure due to development of wound infection.

Four patients had non-serious adverse experiences of urinary tract infection but no clinical response of distant site infection, UTI reported. AN2808 in the cefotetan group had an adverse experience of UTI but no antibiotics were given and no culture taken. The patient is included as a success of prophylaxis. AN3617 in the cefotetan group had an adverse experience of UTI reported but no antibiotics were given for a UTI and no cultures were taken. The patient was given antibiotics for leukocytosis and is captured as a failure of prophylaxis due to inadvertent antibiotic administration. AN3702 in the ertapenem group had an adverse experience of urinary tract infection reported. The clinical response of distant site infection, UTI was reported but not included in database. The patient had a clinical response of distant site infection, pneumonia and an anastomotic leak and is considered a failure of prophylaxis. AN2097 in the cefotetan group had an adverse event of urinary tract yeast infection reported but no clinical response of distant site infection, UTI. The final clinical response for this patient was distant site infection, pneumonia. This patient also had an adverse experience of C*lostridium difficile* infection but no clinical response of distant site infection, other was reported.

Table 15: Proportion of Patients With Distant Site Infections at 4-Weeks Post-Treatment-Displayed by Type of Infection (MITT Population) (Estimated†)

	Treatment Group						
	Ertapenem (A) (N=451)			Cefotetan (B) (N=450)			
	Estimated ᵀ Response			Estimated ᵀ Response			Estimated ᵀ Difference (A - B)
Distant Site Infection	n	%	(95% CI)	n	%	(95% CI)	% (95% CI)
Any Distant Site Infection	48	10.6	(7.8, 13.5)	55	12.3	(9.3, 15.4)	-1.7 (-5.9, 2.5)
Pneumonia	13	2.8	(1.3, 4.4)	23	5.0	(3.0, 7.0)	-2.2 (-4.9, 0.4)
Urinary Tract Infection	20	4.4	(2.5, 6.3)	29	6.4	(4.2, 8.7)	-2.1 (-5.1, 0.9)
Vascular Site Infection	1	0.2	--	0	0.0	--	0.2 --
Other	18	4.0	(2.2, 5.7)	12	2.6	(1.1, 4.1)	1.4 (-1.0, 3.9)

ᵀ Percents and 95% Confidence Intervals computed from a statistical model adjusting for surgical procedure.
Patients could have developed multiple distant site infections. Although a patient may have more than one distant site infection they are counted once in the "Any Distant Site Infection" category.
N = Number of MITT qualified patients in each treatment group.
n = Number of patients with specific distant site infection.
CI = Confidence interval.

Microbiology of Distant Site Infections:

As described in the clinical microbiology procedures, if a patient developed a distant site infection, specimens from the distant site were to be appropriately obtained and sent for aerobic and anaerobic culture. The number (%) of documented pathogens from the distant site is summarized by treatment group for the MITT qualified population in Table 16. Nineteen (19) pathogens were isolated from 14 patients in the ertapenem group and 29 pathogens were isolated from 21 patients in the cefotetan group.

Table 16: Documented Pathogens – Distant Site Displayed by Type of Distant Site Infection (MITT Qualified Population)

	Pneumonia				UTI				Other			
	Ertapenem (N=451)		Cefotetan (N=450)		Ertapenem (N=451)		Cefotetan (N=450)		Ertapenem (N=451)		Cefotetan (N=450)	
	n=2		n=6		n=10		n=13		n=2		n=5	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
All Documented Pathogens	4		8		13		15		2		9	
gram-positive aerobic cocci	2	(50.0)	3	(37.5)	5	(38.5)	9	(60.0)	1	(50.0)	5	(55.6)
Enterococcus	0	(0.0)	0	(0.0)	3	(23.1)	4	(26.7)	0	(0.0)	0	(0.0)
Enterococcus faecalis	1	(25.0)	0	(0.0)	1	(7.7)	3	(20.0)	0	(0.0)	0	(0.0)
Staphylococcus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Staphylococcus aureus	1	(25.0)	1	(12.5)	1	(7.7)	2	(13.3)	1	(50.0)	3	(33.3)
Staphylococcus aureus MRSA	0	(0.0)	0	(0.0)	1	(7.7)	2	(13.3)	0	(0.0)	0	(0.0)
Staphylococcus aureus MSSA	1	(25.0)	1	(12.5)	0	(0.0)	0	(0.0)	1	(50.0)	3	(33.3)
Streptococcus	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Streptococcus pneumoniae	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
gram-positive aerobic bacilli	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)
Gardnerella	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)
gram-negative aerobic bacilli	2	(50.0)	5	(62.5)	7	(53.8)	6	(42.9)	0	(0.0)	3	(33.3)
Enterobacter aerogenes	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)
Enterobacter cloacae	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 16: continued

	Pneumonia				UTI				Other			
	Ertapenem (N=451) n=2		Cefotetan (N=450) n=6		Ertapenem (N=451) n=10		Cefotetan (N=450) n=13		Ertapenem (N=451) n=2		Cefotetan (N=450) n=5	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Escherichia coli	0	(0.0)	1	(12.5)	3	(23.1)	0	(0.0)	0	(0.0)	1	(11.1)
Klebsiella oxytoca	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)
Klebsiella pneumoniae	1	(25.0)	1	(12.5)	1	(7.7)	0	(0.0)	0	(0.0)	1	(11.1)
Proteus mirabilis	0	(0.0)	0	(0.0)	1	(7.7)	1	(7.1)	0	(0.0)	0	(0.0)
Pseudomonas	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pseudomonas aeruginosa	0	(0.0)	2	(25.0)	2	(15.4)	3	(21.4)	0	(0.0)	1	(11.1)
gram-negative aerobic coccobacilli	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
Haemophilus haemolyticus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)
gram-negative cocci	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)
gram-negative coccus	0	(0.0)	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)

The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.
N = Number of MITT Qualified patients in each treatment group.
n = Number of patients with a documented pathogen from each source category in each treatment group.
m = Number of documented pathogens.
% = Number of documented pathogens / all pathogens.

The most frequently documented pathogens were generally consistent with what was seen in the surgical source with *Enterococcus, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli,* being the predominate organisms identified. Additionally, *Pseudomonas aeruginosa* was seen in a higher percentage of distant site infections, primarily in the cefotetan treatment group. There were no anaerobic pathogens identified from the distant site source (Table 17).

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Table 17: Documented Pathogens – Distant Site (MITT Qualified Population)

	Distant site infection source	
	Ertapenem	Cefotetan
	(N=451)	(N=450)
	n=14	n=21
	m (%)	m (%)
All Documented Pathogens	19	29
gram-positive aerobic cocci	8 (42.1)	15 (53.6)
Enterococcus	3 (15.8)	4 (14.3)
Enterococcus faecalis	2 (10.5)	3 (10.7)
Staphylococcus	0 (0.0)	1 (3.6)
Staphylococcus aureus	3 (15.8)	4 (14.3)
Staphylococcus aureus MRSA	1 (5.3)	1 (3.6)
Staphylococcus aureus MSSA	2 (10.5)	3 (10.7)
Streptococcus	0 (0.0)	2 (7.1)
Streptococcus pneumoniae	0 (0.0)	1 (3.6)
gram-positive aerobic bacilli	1 (5.3)	0 (0.0)
Gardnerella	1 (5.3)	0 (0.0)
gram-negative aerobic bacilli	9 (47.4)	13 (46.4)
Enterobacter aerogenes	0 (0.0)	1 (3.6)
Enterobacter cloacae	1 (5.3)	0 (0.0)
Escherichia coli	3 (15.8)	2 (7.1)
Klebsiella oxytoca	0 (0.0)	1 (3.6)
Klebsiella pneumoniae	2 (10.5)	1 (3.6)
Proteus mirabilis	1 (5.3)	1 (3.6)
Pseudomonas	0 (0.0)	1 (3.6)
Pseudomonas aeruginosa	2 (10.5)	6 (21.4)
gram-negative aerobic coccobacilli	0 (0.0)	1 (3.6)
Haemophilus haemolyticus	0 (0.0)	1 (3.6)
gram-negative cocci	1 (5.3)	0 (0.0)
gram-negative coccus	1 (5.3)	0 (0.0)

The number of documented pathogens by pathogen is a count of documented pathogens across all patients/pathogens. This number may be greater than the number of patients due to the possibility of patient having a documented pathogen for more than 1 pathogen/strain.
N = Number of MITT Qualified patients in each treatment group.
n = Number of patients with a documented pathogen from each source category in each treatment group.
m = Number of documented pathogens.
% = Number of documented pathogens/all pathogens.

The in vitro susceptibility results for the pathogens identified from distant site infections for the MITT qualified patients are displayed in separate tables for the two treatment groups; the ertapenem group in Table 18 and the cefotetan group in Table 19. Although the susceptibility results appear to be consistent with what was seen in the surgical source specimens, the limited small number of samples makes meaningful comparisons difficult.

Table 18: In Vitro Susceptibility of Documented Pathogens-Ertapenem Treatment Group Distant Site Infection Source (MITT Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	8	6	4	2	50.0	0	0.0	2	50.0	4	1	25.0	0	0.0	3	75.0
Enterococcus	3	3	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Enterococcus faecalis	2	2	2	0	0.0	0	0.0	2	100.0	2	0	0.0	0	0.0	2	100.0
Staphylococcus aureus	3	3	2	2	100.0	0	0.0	0	0.0	2	1	50.0	0	0.0	1	50.0
Staphylococcus aureus MRSA††	1	1	1	1†	100.0	0	0.0	0	0.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus aureus MSSA††	2	2	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-positive aerobic bacilli	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Gardnerella	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative aerobic bacilli	9	8	5	4	80.0	0	0.0	1	20.0	5	4	80.0	0	0.0	1	20.0
Enterobacter cloacae	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Escherichia coli	3	3	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	2	2	2	2	100.0	0	0.0	0	0.0	2	2	100.0	0	0.0	0	0.0
Proteus mirabilis	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Pseudomonas aeruginosa	2	2	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
gram-negative cocci	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative coccus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-negative cocci	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
gram-negative coccus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

† *Staphylococcus aureus* isolated was resistant to cefotetan and oxacillin by disk diffusion, but demonstrated susceptibility to ertapenem. Accordingly, the isolate should have been resistant to per CSLI guidelines.

†† *Staphylococcus aureus* MRSA (Methicillin-Resistant *Staphylococcus aureus*), MSSA (Methicillin-Sensitive *Staphylococcus aureus*) and Non Spec (Non Specified *Staphylococcus aureus*) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

Table 19: In Vitro Susceptibility of Documented Pathogens- Cefotetan Treatment Group Distant Site Infection Source (MITT Population)

	Total		Ertapenem							Cefotetan						
				S		I		R			S		I		R	
Pathogen	n	N	T	m	%	m	%	m	%	T	m	%	m	%	m	%
gram-positive aerobic cocci	15	12	5	1	20.0	0	0.0	4	80.0	5	1	20.0	0	0.0	4	80.0
Enterococcus	4	4	2	0	0.0	0	0.0	2	100.0	2	0	0.0	0	0.0	2	100.0
Enterococcus faecalis	3	3	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Staphylococcus aureus	4	4	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus aureus MRSA††	1	1	1	0	0.0	0	0.0	1	100.0	1	0	0.0	0	0.0	1	100.0
Staphylococcus aureus MSSA††	3	3	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus	2	2	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Streptococcus pneumoniae	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
gram-negative aerobic bacilli	13	12	3	2	66.7	0	0.0	1	33.3	6	4	66.7	0	0.0	2	33.3
Enterobacter aerogenes	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Escherichia coli	2	2	0	0	0.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Klebsiella oxytoca	1	1	1	1	100.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Klebsiella pneumoniae	1	1	0	0	0.0	0	0.0	0	0.0	1	1	100.0	0	0.0	0	0.0
Proteus mirabilis	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Pseudomonas	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Pseudomonas aeruginosa	6	6	1	0	0.0	0	0.0	1	100.0	2	0	0.0	0	0.0	2	100.0
gram-negative aerobic coccobacilli	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0
Haemophilus haemolyticus	1	1	0	0	0.0	0	0.0	0	0.0	0	0	0.0	0	0.0	0	0.0

†† Staphylococcus aureus MRSA (Methicillin-Resistant Staphylococcus aureus), MSSA (Methicillin-Sensitive Staphylococcus aureus) and Non Spec (Non Specified Staphylococcus aureus) are differentiated based on oxacillin susceptibility results.

n=The number of isolates. N=The number of patients with the pathogen. T = The number of isolates tested. m = The number of isolates tested for each S, I, R under event

%=Number of isolates/number of isolates tested. S = Susceptible. I = Intermediate. R = Resistant.

This table contains counts of pathogens. The total number of pathogens in a pathogen category may include one or more pathogens, not otherwise speciated.

Therefore, totals of specific pathogens may not sum to the total in a pathogen category.

CONCLUSION:

Ertapenem demonstrated in vitro activity against species of *Enterobacteriacae* and *anaerobic bacilli*. Anaerobic bacilli are usually the source of infection in contaminated colorectal surgeries. In addition, ertapenem demonstrated activity against organism associated with skin infections such as *Staphylococcus aureus*, pyogenic *streptococci* as well as anaerobic pathogens.

Pharmacokinetic studies have shown that ertapenem has a half-life of approximately 4 hours; and following a single 1 gram intravenous dose, plasma and interstitial fluid levels are above the MICs of most targeted pathogens. This value is also sustained for 24 hours.

As depicted in the Table 5 below, Protocol 039 demonstrates that a greater proportion of patients who received ertapenem as a 1 gram perioperative dose had a more successful outcome than patients receiving 2 grams of a cefotetan (an FDA approved regimen). The Sponsors' analysis showed that there were 72% of the patients in the evaluable population and 57.2% of the patients in the cefotetan group had a favorable clinical response assessment. The FDA Medial Officer's assessment showed that 70.6% of the patients in the evaluable population and 57.3% of the patients in the cefotetan group had a favorable clinical response assessment.

Table 5

	Ertapenem (A)				**Cefotetan (B)**					
	Estimated[¥] Response				**Estimated[¥] Response**				**Estimated[¥] Difference (A - B)**	
Analysis Set	N	n	%	(95% CI)	N	n	%	(95% CI)	%	(95% CI)
Evaluable										
Applicant	338	243	72.0	(67.2, 76.8)	334	191	57.2	(51.9, 62.6)	14.8	(7.5, 21.9)
Medical Officer	346	244	70.6	(65.8, 75.4)	339	194	57.3	(52.0, 62.6)	13.3	(6.1, 20.4)
MITT										
Applicant	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)
Medical Officer	451	263	58.4	(53.9, 63.0)	450	220	48.8	(44.2, 53.5)	9.6	(3.1, 16.0)

[¥] Computed from a statistical model adjusting for surgical procedure.

N = Number of Evaluable patients in each treatment group.

n = Number of Evaluable patients with a favorable clinical response each treatment group.

CI = Confidence interval.

Applicant's results for Evaluable and MITT from Tables 7-1 (p. 99) of the CSR and the 4/27/06 Information Amendment, respectively.

Therefore, from a microbiology perspective based on analysis of information provided by the Applicant, the Reviewer recommends approval of the use of ertapenem as for the prophylaxis for colorectal surgery. Ertapenem was shown to have activity against those organisms commonly associated with infections following colorectal surgery.

DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

PACKAGE INSERT:

No changes to the Microbiology portion of the package insert for ertapenem will be made.

Microbiology

Ertapenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta-lactamases. Ertapenem has been shown to be active against most isolates of the following microorganisms *in vitro* and in clinical infections. (See INDICATIONS AND USAGE):
Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus (methicillin susceptible isolates only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)
Streptococcus pyogenes
Note: Methicillin-resistant staphylococci and *Enterococcus* spp. are resistant to ertapenem.
Aerobic and facultative gram-negative microorganisms:
Escherichia coli
Haemophilus influenzae (Beta-lactamase negative isolates only)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis
Anaerobic microorganisms:
Bacteroides fragilis
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Clostridium clostridioforme
Eubacterium lentum
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella bivia
The following *in vitro* data are available, **but their clinical significance is unknown**.

DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-337 SLR 021
DATE REVIEW COMPLETED: July 12, 2006
INVANZ Clinical Microbiology Review

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem; however, the safety and effectiveness of ertapenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

Aerobic and facultative gram-positive microorganisms:
Staphylococcus epidermidis (methicillin susceptible isolates only)
Streptococcus pneumoniae (penicillin-intermediate isolates only)

Aerobic and facultative gram-negative microorganisms:
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae (Beta-lactamase positive isolates)
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic microorganisms:
Bacteroides vulgatus
Clostridium perfringens
Fusobacterium spp.

Susceptibility Tests Methods:
When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method[1,2] or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 4.

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg ertapenem to test the

susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria should be interpreted according to criteria provided in Table 4.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to ertapenem as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to criteria provided in Table 4.

Table 4
Susceptibility Interpretive Criteria for Ertapenem

Pathogen	Minimum Inhibitory Concentrations[a] MIC (µg/mL)			Disk Diffusion[a] Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae and *Staphylococcus* spp.	≤2.0	4.0	≥8.0	≥19	16-18	≤15
Haemophilus spp.	≤0.5	-	-	≥19	-	-
Streptococcus pneumoniae [b,c]	≤1.0	-	-	≥19	-	-
Streptococcus spp. other than *Streptococcus pneumoniae* [d,e]	≤1.0	-	-	≥19	-	-
Anaerobes	≤4.0	8.0	≥16.0	-	-	-

[a] The current absence of data in resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

[b] *Streptococcus pneumoniae* that are susceptible to penicillin (penicillin MIC ≤0.06 µg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[c] *Streptococcus pneumoniae* that are susceptible to penicillin (1-µg oxacillin disk zone diameter ≥20 mm), can be considered susceptible to ertapenem. Isolates with 1-µg oxacillin zone diameter ≤19 mm should be tested against ertapenem using an MIC method.

[d] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤0.12 µg/mL) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

[e] *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (10-units penicillin disk zone diameter ≥24 mm), can be considered susceptible to ertapenem. Isolates with 10-units penicillin disk zone diameter <24 mm should be tested against ertapenem using an MIC method.

Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci and they should not be tested against ertapenem.

Note: *Staphylococcus* spp. can be considered susceptible to ertapenem if the penicillin MIC is ≤0.12 μg/mL. If the penicillin MIC is >0.12 μg/mL, then test oxacillin. *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin MIC is ≤2.0 μg/mL and resistant to ertapenem if the oxacillin MIC is ≥4.0 μg/mL. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin MIC is ≤0.25 μg/mL and resistant to ertapenem if the oxacillin MIC ≥0.5 μg/mL.

Staphylococcus spp. can be considered susceptible to ertapenem if the penicillin (10 U disk) zone is ≥29 mm. If the penicillin zone is ≤28 mm, then test oxacillin by disk diffusion (1μg disk). *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin (1μg disk) zone is ≥13 mm and resistant to ertapenem if the oxacillin zone is ≤10 mm. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin zone is ≥18 mm and resistant to ertapenem if the oxacillin (1μg disk) zone is ≤17 mm.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures[1,2,3,4]. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant. Standard ertapenem powder should provide the following range of values noted in Table 5.

Table 5
Acceptable Quality Control Ranges for Ertapenem

Microorganism	Minimum Inhibitory Concentrations MIC Range (µg/mL)	Disk Diffusion Zone Diameter (mm)
Escherichia coli ATCC 25922	0.004-0.016	29-36
Haemophilus influenzae ATCC 49766	0.016-0.06	27-33
Staphylococcus aureus ATCC 29213	0.06-0.25	-
Staphylococcus aureus ATCC 25923	-	24-31
Streptococcus pneumoniae ATCC 49619	0.03-0.25	28-35
Bacteroides fragilis ATCC 25285	0.06-0.5[f] 0.06-0.25[g]	-
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0[f] 0.25-1.0[g]	-
Eubacterium lentum ATCC 43055	0.5-4.0[f] 0.5-2.0[g]	-

[f] Quality control ranges for broth microdilution testing
[g] Quality control ranges for agar microdilution testing

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SUMMARY AND RECOMMENDATIONS:

From the microbiology perspective, based on analysis of the information provided by the applicant, the Reviewer recommends approval of prophylactic use of ertapenem for colorectal surgery.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	21-337 (SE1-021)
PRODUCT	Ertapenem sodium (Invanz™)
FORMULATION	Sterile lyophilized powder for injection, 1 gram
SUBMISSION DATE	November 9, 2005
SUBMISSION TYPE	Efficacy supplement
SPONSOR	Merck & Co., Inc., West Point, PA 19486
OCP DIVISION	Division of Clinical Pharmacology 4
MEDICAL DIVISION	Division of Anti-Infective and Opthalmologic Products
REVIEWER	Charles R. Bonapace, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

BACKGROUND:

Ertapenem is a 1-β-methyl carbapenem that has *in vitro* activity against many common aerobic and anaerobic Gram-positive and Gram-negative pathogens including *Streptococcus* species, methicillin-susceptible staphylococci, the (b) (4) and many anaerobic species. It is approved in the U.S. for the treatment of moderate to severe infections caused by susceptible organisms due to the following indications: Complicated intra-abdominal infections, complicated 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. The approved dosage regimen of ertapenem in patients 13 yrs of age and older is 1 gram administered once daily by intravenous (IV) infusion for up to 14 days or intramuscular injection for up to 7 days.

Postoperative infection is a common complication of surgical procedures. Antimicrobial prophylaxis prior to colon surgery reduces both postoperative infection rate and mortality. The optimal timing of IV administration of antimicrobial agents is close to the time of incision (generally 30 to 60 min before), so that maximum serum and tissue concentrations are achieved when the skin has first been opened. Adequate serum concentrations, exceeding the MIC of the likely pathogens, should be present for the duration of the operation, and importantly, immediately prior to wound closure.

In the current submission, the sponsor conducted a Phase 3, prospective, multicenter, double-blind, randomized comparative clinical trial (Study P039) to evaluate the safety, efficacy and tolerability of ertapenem versus cefotetan for prophylaxis of surgical site infection following elective colorectal surgery in patients ≥ 18 years of age. Patients were randomized to receive a single prophylactic dose of either ertapenem (1 gram) or cefotetan (2 grams) within 30-60 min prior to the planned initial surgical incision and were followed for 4-weeks postoperatively for failure of prophylaxis. Based on the Cefotan® (cefotetan disodium) approved label, the recommended dosage of cefotetan for prophylaxis is 1 to 2 grams administered once 30-60 min prior to surgery. Thus, the proposed use and dose of cefotetan in the current study is consistent with the approval label.

Although the protocol for the Phase 3 study stated that patients were to receive a single prophylactic dose of either antibiotic 30-60 min prior to the planned initial surgical incision and within 6 hrs of skin closure, 148/346 (42.8%) evaluable patients in the ertapenem arm and 119/339 (35.1%) evaluable patients in the cefotetan arm received study medication >60 min prior to the surgical incision. Clinical pharmacology was consulted to evaluate the possibility that administration of the antibiotics >60 min prior to the surgical incision could have altered the results of the study such that ertapenem was favored over

cefotetan. Thus, the reviewer performed a pharmacokinetic/pharmacodynamic (PK/PD) analysis to determine the time (in hrs) unbound concentrations of each drug remained above the MIC of four common pathogens while varying the elapsed time between the start of the infusion and the start of surgery. The results from this analysis were compared to the percentage of patients with a favorable clinical response in an attempt to explain the results of the Phase 3 study.

DATA:
Plasma concentration-time data for ertapenem were obtained from Study P039 of NDA 21-337 (refer to the review of the original NDA dated November 8, 2001 for further details) in which eight male and eight female healthy subjects (n=16) received a single 1 gram dose of ertapenem IV infused over 30 min. Blood samples for ertapenem concentration determination were obtained at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 18, and 24 hrs following the start of the infusion.

Since plasma concentration-time data were not available for cefotetan, pharmacokinetic parameters for cefotetan were obtained from published literature. In a study by Nakagawa K et al. (1), 500 mg and 1000 mg cefotetan IV was administered as a bolus injection to six subjects and fit to a 2-compartment pharmacokinetic model. The values for V_1, K_{10}, K_{12}, and K_{21} were 3.95 L, 0.47 hr^{-1}, 1.52 hr^{-1} and 1.50 hr^{-1}, respectively following the administration of 1000 mg cefotetan.

Minimum inhibitory concentration (MIC_{90}) data for the two drugs were obtained from available sources. For ertapenem, MIC data were obtained from an efficacy supplement (SE1-019) for NDA 21-337 submitted December 17, 2004 to add the indication of diabetic foot infections in adults to the label. For cefotetan, MIC data were obtained from the action package for NDA 50-588, approved December 27, 1985. The MIC_{90} value for *Bacteroides fragilis* was obtained from a published study by Owens WE et al. (2). A comparison of the MIC_{90} values for both drugs against clinically relevant pathogens for postoperative infections is shown in Table 1.

Table 1. MIC_{90} values for ertapenem and cefotetan against common pathogens

Organism	Ertapenem		Cefotetan	
	N	MIC_{90} (μg/mL)	N	MIC_{90} (μg/mL)
Staphylococcus aureus	375	0.25	57	8
Escherichia coli	254	0.016	2982	0.5
Bacteroides fragilis	401	1	26	128
Streptococcus agalactiae[1]	206	0.06	117	4[a]

a-*Streptococcus pyogenes* and *Streptococcus agalactiae* isolates combined (N=117)

DATA ANALYSIS:
Ertapenem plasma concentration-time data for each subject were fit to a two-compartment pharmacokinetic model with zero-order input and first-order elimination using WinNonlin version 5.0.1. A weighting factor of 1/Y was used to fit the data. The parameters estimated were V_1, K_{10}, K_{12}, and K_{21}. The individual pharmacokinetic parameters were used to simulate plasma concentrations following a single dose of 1000 mg infused over 30 min. Unbound plasma concentrations were calculated using the protein binding of ertapenem in the approved label (95%) to correct total plasma concentrations. The mean plasma concentration at each time point was calculated based on the simulated profiles from 16 subjects.

The mean cefotetan pharmacokinetic parameters obtained from the literature were used to simulate plasma concentrations following a single dose of 2000 mg infused over 30 min. Unbound plasma concentrations were calculated using the protein binding of cefotetan in the approved label (88%) to correct total plasma concentrations.

The primary data analysis was the calculation of time (in hrs) that the unbound plasma concentration of each drug exceeded the MIC_{90} of the four pathogens from the start of the surgery. The analysis takes into account the different pharmacokinetics, protein binding, and potency (MIC_{90} values) of the two drugs as well as variable times between the start of the infusion and the initiation of surgery. The results can be compared to the recommendations for preoperative prophylaxis of surgical infections which state that adequate serum concentrations, exceeding the MIC of the likely pathogens, should be present for the duration of the operation, including when the skin is first opened and immediately prior to wound closure.

RESULTS:

The observed mean plasma concentration-time profile of ertapenem IV 1 gram infused over 30 min from healthy subjects and the simulated mean plasma concentration-time profile of ertapenem IV 1 gram infused over 30 min were nearly superimposable (data not shown). The observed plasma concentrations of ertapenem were adequately characterized by a two-compartment pharmacokinetic model.

The mean simulated unbound plasma concentration-time profiles in relation to the MIC_{90} values against four common pathogens are shown in Figure 1 for ertapenem and Figure 2 for cefotetan. Plasma concentrations are shown in blue and MICs are shown in red. Although the mean unbound concentrations of cefotetan were higher than ertapenem, the MIC_{90} values of cefotetan for these organisms were higher than those of ertapenem and the MIC_{90} of *B. fragilis* exceeding the mean unbound C_{max} of cefotetan by several fold.

Figure 1. Mean unbound simulated plasma concentration-time profile for <u>ertapenem</u> IV 1 gram infused over 30 min and corresponding MIC values

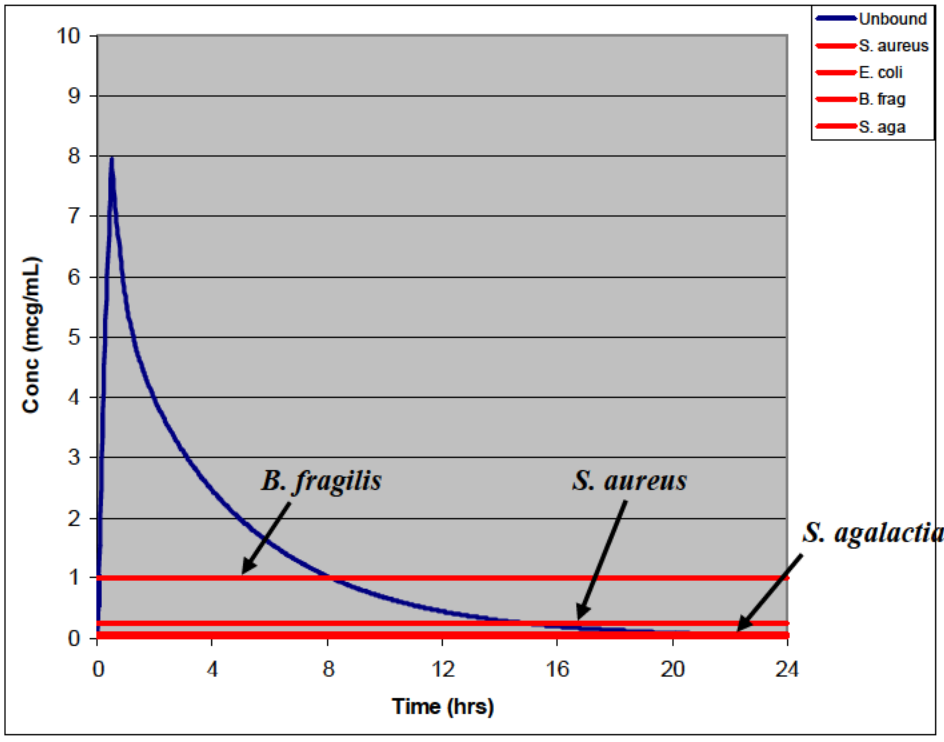
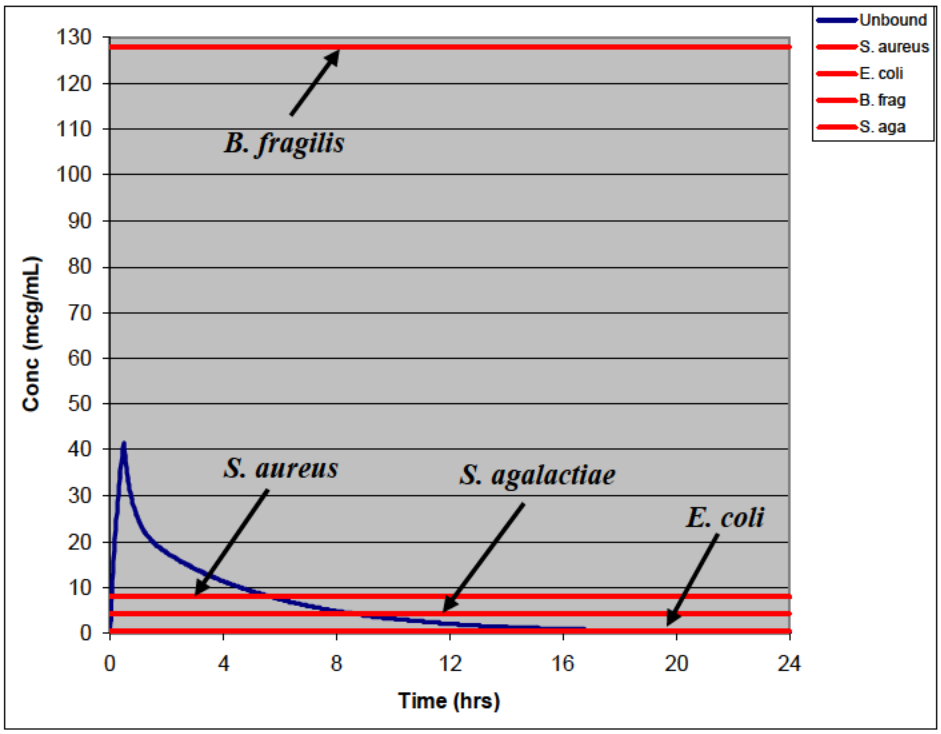


Figure 2. Mean unbound simulated plasma concentration-time profile for cefotetan IV 2 grams infused over 30 min and corresponding MIC values



The mean duration of time (in hrs) that the unbound concentrations of ertapenem and cefotetan remained above the MIC_{90} after the initiation of the surgical incision is shown in Table 2. The protocol for Study P039 stated that patients were to receive a single prophylactic dose of either antibiotic 30-60 min prior to the initial surgical incision and within 6 hrs of skin closure. As shown in the table, the mean unbound concentration of ertapenem exceeded the MIC_{90} of all four pathogens for at least 7.1 hrs if the protocol was followed (within 60 min prior to the surgical incision) and at least 6.1 hrs if the antibiotic infusion was delayed 1 hr (within 2 hrs prior to the surgical incision).

The mean unbound concentrations of cefotetan exceeded the MIC_{90} for at least 7.9 hrs with *E. coli* and *S. agalactiae* if the drug infusion was initiated within 60 min prior to the surgical incision and at least 6.9 hrs if the drug infusion was initiated within 2 hrs (delayed 1 hr) prior to the surgical incision. Unlike ertapenem, the mean unbound concentrations of cefotetan never exceeded the MIC_{90} for *B. fragilis* and exceeded the MIC_{90} for *S. aureus* for only 4.6 hrs if the protocol was followed and 3.6 hrs if the surgical incision was delayed 1 hr (within 2 hrs prior to the surgical incision).

Table 2. Mean duration of time that unbound concentrations remain above the MIC_{90} following the surgical incision

Elapsed time from start of infusion to surgical incision (hrs)	*S. aureus*	*E. coli*	*B. fragilis*	*S. agalactiae*
	Ertapenem 1 gram			
Ertapenem 1 gram IV				
1 hr	13.8 hrs	>24.0 hrs	7.1 hrs	20.9 hrs
2 hrs	12.8 hrs	> 24.0 hrs	6.1 hrs	19.9 hrs
4 hrs	10.8 hrs	>24 .0 hrs	4.1 hrs	17.9 hrs
6 hrs	8.8 hrs	>24.0 hrs	2.1 hrs	15.9 hrs
Cefotetan 2 grams IV				
1 hr	4.6 hrs	17.5 hrs	0.0 hrs	7.9 hrs
2 hrs	3.6 hrs	16.5 hrs	0.0 hrs	6.9 hrs
4 hrs	1.6 hrs	14.5 hrs	0.0 hrs	4.9 hrs
6 hrs	0.0 hrs	12.5 hrs	0.0 hrs	2.9 hrs

For the evaluable population, 72.5% of patients in the ertapenem group and 57.2% of patients in the cefotetan group had a favorable clinical response assessment. The difference in the clinical response rates between the two treatment groups was 13.3 percentage points favoring ertapenem with a 95% CI of 6.1% to 20.4%. The percentage of patients with a favorable clinical response stratified by the time from the start of the study drug infusion to the start of surgery is shown in Table 3. The clinical response did not appear to be related to the elapsed time from the start of the infusion to the start of the surgery for either drug. In fact, the clinical response rate was higher for patients in the cefotetan arm when the elapsed time from the start of the infusion to the start of the surgery was >60 min compared to ≤60 min.

Table 3. Proportion of patients with a favorable clinical response stratified by time from start of study medication to the start of surgery

Time from start of infusion to start of surgery	Ertapenem (N=346)		Cefotetan (n=339)		Observed difference % (95% CI)
	n/N	% Response	n/N	% Response	
≤60 min	141/198	71.2%	123/220	55.9%	15.3 (6.1, 24.2)
>60 min	103/148	69.6%	71/119	59.7%	9.9 (-1.6, 21.4)
Overall	244/346	70.5%	194/339	57.2%	13.3 (6.1, 20.4)

n/N = number of evaluable patients with a favorable assessment/number of evaluable patients with assessment

The elapsed time from the start of the antibiotic infusion to the end of surgery was >4 hrs for 73/346 (21%) evaluable patients in the ertapenem arm and 64/339 (19%) evaluable patients in the cefotetan arm. However, the percentage of patients with a favorable clinical response appeared to be related to the time from the start of the infusion to the end of surgery for cefotetan but not for ertapenem (Table 4). When the elapsed time exceeded 4 hrs, the clinical response for cefotetan was only 40.6% compared to 61.1% when the elapsed time did not exceed 4 hrs.

Table 4. Proportion of patients with a favorable clinical response stratified by time from start of study medication to the end of surgery

Time from start of infusion to end of surgery	Ertapenem (N=346)		Cefotetan (n=339)		Observed difference % (95% CI)
	n/N	% Response	n/N	% Response	
≤4 hrs	195/273	71.4%	168/275	61.1%	10.3 (2.4, 18.1)
>4 hrs	49/73	67.1%	26/64	40.6%	26.5 (9.8, 41.8)
Overall	244/346	70.5%	194/339	57.2%	13.3 (6.1, 20.4)

n/N = number of evaluable patients with a favorable assessment/number of evaluable patients with assessment

The time that an antibiotic needs to exceed the MIC of a pathogen is dependent upon the time between the start of the infusion and the start of the surgery, the duration of the surgical procedure, and the MIC values of each pathogen. The data in Table 2 supports the results observed in Tables 3 and 4. Delaying the start of surgery following administration of the antibiotic may impact the clinical response if the duration of the surgical procedure outlasts the duration of the time that the unbound concentration of the antibiotic exceeds the pathogen's MIC. Considering the PK/PD data for both antibiotics, delaying the surgical incision following infusion of the antibiotic may impact the efficacy of cefotetan to a greater extent than ertapenem. However, the length of the surgical procedure and pathogen susceptibility are likely to have a greater impact on the clinical response than delaying the start of surgery.

CONCLUSIONS:

Although 42.8% of evaluable patients in the ertapenem group and 35.1% of evaluable patients in the cefotetan group received a prophylactic dose of antibiotic >60 min prior to the surgical incision, the patients in the cefotetan group are more likely to be impacted by the delay. However, the length of the surgical procedure and pathogen susceptibility may be greater determinants of the clinical response. Thus, the delay between administration of the antibiotic and start of surgery does not appear to have influenced the overall clinical efficacy of cefotetan relative to ertapenem. An exception may be patients with long surgical procedures (>3-4 hrs) since the duration from the start of the infusion to the end of surgery was further extended by delaying the start of surgery.

COMMENTS:

1. The MIC_{90} data for cefotetan were obtained from the original action package (December 1985) and may underestimate current MIC values. The use of this information results in a conservative approach since it may overestimates the activity of cefotetan. However, the difference in favorable outcome observed for ertapenem and cefotetan was supported by the PK/PD analysis and the difference may be even greater if current MIC_{90} values were utilized.

REFERENCES:

1. Nakagawa K, Koyama M, Tachibana A, Komiya A, Kikuchi Y, Yano K. Pharmacokinetics of cefotetan (YM09330) in humans. Antimicrob. Agents Chemother. 1982;22(6):935-941.

2. Owens WE, Finegold SM. Comparative in vitro susceptibilites of anaerobic bacteria to cefmenoxime, cefotetan, and N-formimidoyl thienamycin. Antimicrob. Agents Chemother. 1983:23(4):626-629.

RECOMMENDATIONS:
This application was reviewed by the Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 and found to be acceptable from a clinical pharmacology point of view.

_____

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT Initialed by Venkat R. Jarugula, Ph.D., Team Leader_____

cc:
Division File: NDA 21-337 (S-021)
HFD-520 (CSO/Dillon-Parker)
HFD-520 (MO/Mulinde, Kim)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm.)

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/s/

Charles Bonapace
6/29/2006 07:59:18 AM
BIOPHARMACEUTICS

Venkateswar Jarugula
6/29/2006 12:48:43 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

OTHER REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: August 07, 2006

To: Susmita Samanta, Project Manager
Peter Kim, M.D., Clinical Reviewer
Division of Anti-infective and Ophthamology Products

From: Sheila Ryan, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: Invanz (ertapenem for injection)
NDA 21-337/S021

DDMAC has reviewed the proposed product labeling (PI) for Invanz and we offer the following comments. We are including comments on the Clinical Studies section, revised as of 8-4-06 and the proposed label, revised as of 7-24-06. Please feel free to contact me with any questions or clarifications.

COMMENTS regarding the CLINICAL STUDIES section (revised as of 8-4-06):

(b) (4)

2 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

Sheila Ryan
8/7/2006 03:57:36 PM
DDMAC REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-337/S-021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-337 SUPPL # 021 HFD # 520

Trade Name Invanz

Generic Name Ertapenem sodium

Applicant Name Merck & Co., Inc.

Approval Date, If Known 8/10/06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

NA

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-337 11/21/01

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

NA

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

NA

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 039 was a multicenter, randomized, double-blind trial that compared a single dose of ertapenem 1 gram IV with cefotetan 2 gram IV for the prophylaxis of surgical site infection following elective colorectal surgery.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NA

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 039 was a multicenter, randomized, double-blind trial that compared a single dose of ertapenem 1 gram IV with cefotetan 2 gram IV for the prophylaxis of surgical site infection following elective colorectal surgery.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 48,485	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Susmita Samanta
Title: Regulatory Project Manager
Date: 11/9/06

Name of Office/Division Director signing form: Janice Soreth, M.D.
Title: Director, Division of Anti-Infective and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Janice Soreth

11/9/2006 02:39:13 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 25, 2006

TO: Jeffrey R. Tucker, M.D., Merck & Co., Inc.

THROUGH : Yunfan Deng, PhD, Statistical Reviewer

FROM: Susmita Samanta, MD, Regulatory Project Manager

SUBJECT: NDA 21-337/S-021, INVANZ™ (ertapenem sodium)

Indication: Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery

Statistical Comment:

We recognize that you discussed with us about the choice of non-inferiority margin during our previous communications. However, we have been unable to locate any written documentation in our archive as to the appropriateness of the pre-specified non-inferiority margins used in your phase 3 study for the above indication. Please provide scientific justification for your choice of non-inferiority margin for this study or direct us to its location in the submission. According to your submitted data and analysis, we understand that INVANZ™ has demonstrated evidence based on the primary hypothesis of non-inferiority. However, it is necessary for you to provide us with scientific justification for the choice of non-inferiority margin. This information would be helpful in completing our review.

As discussed in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials" (located at www.fda.gov/cder/guidance/index.htm) a non-inferiority margin should be defined as "the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator." It "cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial." Furthermore, 21CFR314.126(b)(2)(iv) states the following:

> If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

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/s/

Susmita Samanta
5/25/2006 09:53:13 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-337 Supplement # 021 Efficacy Supplement Type SE- 1

Trade Name: Invanz
Established Name: ertapanem sodium
Strengths: 1 gm

Applicant: Merck & Co.
Agent for Applicant: Jeffrey R. Tucker, MD

Date of Application: 11/9/05
Date of Receipt: 11/10/05
Date clock started after UN: NA
Date of Filing Meeting: 12/13/05
Filing Date: 1/9/06
Action Goal Date (optional): 9/8/06 User Fee Goal Date: 9/8/06

Indication(s) requested: Prophylaxis of surgical site infection following elective colorectal surgery

Type of Original NDA: (b)(1) X (b)(2) ☐
OR
Type of Supplement: (b)(1) X (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

X NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S X P ☐
Resubmission after withdrawal? NA Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) NA

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES X NO ☐
  If yes, explain: The original NDA has exclusivity, this is a supplement

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES X NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? The whole NDA except the forms and the certifications

  Additional comments: NA

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance?
  N/A ☐ YES X NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES X NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments: NA

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X[NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 48,485

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO X
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO X

- Risk Management Plan consulted to ODS/IO? N/A X YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO X

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO X

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12/13/05

BACKGROUND: Invanz is already approved in 2001. This is a supplement for a new indication. (Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Janice Soreth, Jean Mulinde, Peter Kim, Fred Marsik, Connie Mahon, Thamban Valappil, Yunfan Deng, Swapan De, Wendy Schmidt, Bob Osterberg and Venkat Jarugula

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Peter Kim
Secondary Medical:	Jean Mulinde
Statistical:	Yunfan Deng
Pharmacology:	NA
Statistical Pharmacology:	NA
Chemistry:	Swapan De
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Chuck Bonapace
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	Connie Mahon
DSI:	Mathew Thomas
Regulatory Project Management:	Susmita Samanta
Other Consults:	NA

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO X
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE X REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO X

PHARMACOLOGY N/A X FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
- Microbiology YES X NO ☐

ELECTRONIC SUBMISSION:
Any comments: NO

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.X Convey document filing issues/no filing issues to applicant by Day 74.

Susmita Samanta
Regulatory Project Manager, HFD-520

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/s/

Susmita Samanta
4/13/2006 10:04:15 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-337/S-021

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your November 9, 2005, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invanz™ (Ertapenem Sodium).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on January 9, 2006, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any question, call Susmita Samanta, M.D., Regulatory Project Manager, at (301) 796-1400.

Sincerely yours,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker
1/6/2006 12:43:05 PM
NDA 21-337/S-021

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-337/S-021 **INFORMATION REQUEST LETTER**

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your November 9, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invanz™ (Ertapenem Sodium).

We are reviewing your submission and based on a blinded review of approximately 30% of the case report forms (CRFs), we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

EVALUABILITY:

1. You have considered the following patients nonevaluable for the per protocol analysis due to prior or concomitant antibiotic violations: 2858, 2859, 2233, 2636, 2947, 2481, 2637, and 2853. However, on further review of the following sections of the Clinical Study Report (CSR): section 5.5.3.1 "Success of Prophylaxis" on page 45, section 5.5.3.2 "Unexplained antibiotic use" on page 47, section 5.4.6 "Prior and Concomitant Therapy" on page 43, and section 5.3.2 Exclusion criteria "i" on page 39, it would appear that the previously listed patients are evaluable.

   Provide further clarification if you still consider these patients nonevaluable for the per protocol analysis. If the patients are evaluable then make the appropriate changes to pertinent analyses (including the analyses requested by the Division on 12/21/05) and determine if other patients in the CRF index fall into this situation and correct evaluability accordingly.

2. You considered the following patients nonevaluable for the per protocol analysis due to 4-week follow-up window violation: 2624 and 2875. However, based on the section titled "Evaluable Patients at the 4-Week Posttreatment Follow-Up Assessment" on page 1451 of the CSR, it would appear that the previously listed patients are evaluable.

Specifically, Patient 2624 had surgery on (b) (6) and was deemed a failure by the investigator on (b) (6). The patient was noted to have wound dehiscence and received antibiotics (keflex (b) (6) and amoxicillin (b) (6)) for an abdominal fluid collection. Therefore, according to page 1451, the failure should carry forward. Patient 2875 had a 4-week follow-up visit within the 60-day limit noted on page 1451 of the CSR.

Provide further clarification if you still consider these patients nonevaluable for the per protocol analysis. If the patients are evaluable then make the appropriate changes to pertinent analyses (including the analyses requested by the Division on 12/21/05) and determine if other patients in the CRF index fall into this situation and correct evaluability accordingly.

3. You considered Patient 2924 nonevaluable for the per protocol analysis due to minimal disease definition not met. However, the patient was reported as having adequate bowel preparation and received study medication. This patient was also reported as nonevaluable due to distant site infection with concomitant antibiotic administration and no evidence of subsequent wound infection. The patient's surgical procedure was reported as "rectectomy." The patient developed peri-rectal drainage during the post-operative period and was treated with Zosyn from (b) (6). This would appear to constitute a surgical site infection that required antibacterial therapy. Therefore this patient would appear to be an evaluable failure for both the per protocol and MITT analyses.

   Please provide further clarification if you still consider this patient nonevaluable. If the patient is evaluable then make the appropriate changes to the pertinent analyses (including the analyses requested by the Division on 12/21/05) and determine if other patients in the CRF index fall into this situation and correct evaluability accordingly.

ADDITIONAL QUERIES:

1. Patient 2156 reportedly had a urinary tract infection (UTI) that caused the patient to prematurely discontinue from the study; however, we could not find any evidence for a UTI in the CRF. Urinalyses from (b) (6) and (b) (6) did not show evidence of infection even though the patient was noted to be febrile from (b) (6) There is no record of a urine culture in the CRF. Antibacterial therapy (Zosyn) was started on (b) (6). Please provide evidence of a UTI or other etiology for the patient's febrile illness that required antibacterial therapy.

2. Provide the reason why Patient 2131 was deemed a study therapy violation and therefore was nonevaluable for the per protocol analysis.

3. Patient 2396 was deemed nonevaluable due to a prior or concomitant antibiotic violation. Please identify the antibiotic that caused the violation.

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker
1/6/2006 01:19:38 PM
NDA 21-337/S-021 Information Request Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-337/S-013 **INFORMATION REQUEST LETTER**

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your November 9, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INVANZ™ (Ertapenem Sodium) Injection, 1 gm.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

Please run the following sensitivity analyses:

- For Clinical efficacy for both the Evaluable Per Protocol study population and the MITT study population:

  1. Please stratify results on whether the duration from start of study therapy infusion to end of surgery is < or = 4 hrs versus those patients whose duration was > 4 hrs.

  2. Please stratify results on whether the duration from start of study therapy infusion to start of surgery is < or = 60 mins versus those patients whose duration was > 60 mins.

Microbiology

Provide line listings of microbiology data from the phase 3 clinical studies (Protocol 039). Each column heading should be identified with respect to the scope of information below it. The Division recommends that the Applicant include the following information under appropriate columnar headings:

- Patient ID number
- Species of bacterial isolate
- Clinical Sample (Source of isolate)
- Microscopy results (Direct smear exam). Provide the identification of organisms identified from each cultured sample
- Patient's clinical and microbiological response
- In vitro Susceptibility testing results (MIC) for the test drug and comparator drug for each organism isolated from patients considered clinical and/or microbiological failures
- In vitro Susceptibility test results (MIC) for the test drug and comparator drug for each isolated organisms from distant sites
- In vitro Susceptibility test results (MIC_{50} and MIC_{90}) from recent surveillance clinical isolates for the test drug and comparator
- Quality control data from the laboratories that performed the susceptibility studies in the clinical trials

The Division recommends that you provide the following in separate tabular format:

- All MIC and patient clinical and bacteriological responses for each pathogen for the proposed indication. The Applicant should list all subsets of organisms demonstrating unique mechanisms of resistance (e.g. methicillin-resistant *Staphylococcus aureus).*
- For each organism (species and subspecies), the MIC value indicating the number and percent of isolates at that MIC associated with each bacteriological and clinical response.
- For each organism (species and subspecies), the Agency recommends that the Applicant provide in a graphical format (histograms, scattergram) comparing the number of isolates from clinical studies at each MIC with those from laboratory isolates tested. Organisms with characterized phenotypic resistance should be presented as a subset.

The following additional microbiology information is requested:

- Detailed descriptions of methods on specimen collection, transport, preservation and processing to include those that pertain to fastidious organisms
- Criteria for specimen acceptability or rejection.
- Methods for microscopic evaluation of direct smear and criteria used for interpretation should be included in the protocol. Please provide the procedures for culturing and culture interpretation, methods for identification and susceptibility testing of isolates.

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Susmita Samanta
12/21/2005 11:14:09 AM
Signing for Frances Lesane

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: YES NO

NDA 21-337: MERCK's INVANZ for Prevention (Prophylaxis) Against Surgical Site Infections in Elective Colorectal Surgery Patients, Comparator = Cefotetan

CLINICAL:

(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the clinical section of the NDA legible so that substantive review can begin? ✓

(4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? ✓

(5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? ✓

(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? ✓

(6) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested? ✓

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? ✓

(8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? ✓

(9) Has the application submitted a rationale for assuming the applicability of foreign data in the submission to the US population? N/A

(10) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? ✓

(11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? ✓

(12) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product? ✓

(13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? ✓

(14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? ✓

(15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. ✓

Reviewing Medical Officer

Supervisory Medical Officer

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/s/

Peter Kim
12/7/2005 09:03:04 AM
MEDICAL OFFICER

Jean Mulinde
12/7/2005 10:40:21 AM
MEDICAL OFFICER